

Lateral inhibition in the inner retina is important for spatial tuning of ganglion cells

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The center-surround receptive-field organization in retinal ganglion cells is widely believed to result mainly from lateral inhibition at the first synaptic level (in the outer retina). Inhibition at the second synaptic level (in the inner retina) is thought to mediate more complex response properties. Here we show that much of the sustained surround antagonism in certain on-center ganglion cells results from lateral inhibition in the inner retina, via GABAergic amacrine cells, and that the lateral conduction of this signal requires voltage-gated sodium currents. Blocking lateral inhibition in the inner retina eliminates the preference of small-center ganglion cells for small stimuli but has little effect on ganglion cells with large receptive-field centers. These results illustrate how lateral inhibition at successive synaptic stages can selectively control the size of neural receptive-field centers.

Spatial resolution and gain control are important sensory-system functions that frequently involve lateral inhibition, which can increase spatial tuning of a neuron by effectively reducing the area of its receptive-field center. In the vertebrate retina, lateral inhibition can modulate the direct pathway for light-evoked signals (photoreceptors to bipolar cells to ganglion cells) both via horizontal cells in the outer retina, where photoreceptors synapse onto bipolar cells, and via amacrine cells in the inner retina, where bipolar cells synapse onto ganglion cells. One function of horizontal cells is the modulation of synaptic gain between photoreceptors and bipolar cells¹. Because horizontal cells have large receptive fields, this causes the classic sustained 'center-surround' antagonistic receptive-field organization of bipolar cells¹⁻⁴. Many ganglion cells have a similar receptive-field organization^{5,6}, which is thought to be mainly due to the lateral inhibition in the outer retina. This view is supported by the finding that hyperpolarizing current injection into horizontal cells, which mimics their response to light, elicits a 'surround-like' response in ganglion cells^{7,8}.

Inhibitory interactions via amacrine cells in the inner retina typically mediate more complex functions, such as directional selectivity and responses specifically related to changing or moving light stimuli^{3,9-16}. Although an inner retinal contribution to steady surround responses has been suggested^{16,17}, the extent to which this affects the size of the receptive-field center (spatial tuning) of ganglion cells has not been studied. Here we show in the tiger salamander retina that much of the sustained surround antagonism in on-center ganglion cells, particularly those with small receptive-field centers, is due to lateral inhibition in the inner retina. This inhibition is mediated by GABAergic amacrine cells, and the lateral spread of this signal through amacrine cell processes requires voltage-gated sodium currents. The functional significance of this lateral inhibition at the second synaptic level is to significantly and selectively sharpen the spatial tuning of ganglion cells.

Results

Because many amacrine cells fire action potentials, whereas outer retinal neurons do not, we reasoned that if there were an inner retinal contribution to sustained surround antagonism, it might be mediated by action potentials. We therefore sought to determine whether a component of the sustained surround antagonism in ganglion cells could be blocked by tetrodotoxin (TTX), which blocks voltage-dependent sodium channels. One consequence of surround antagonism is found in a cell's spatial tuning (that is, preference for stimuli of a certain size). Increasing the size of a spot stimulus centered on the receptive field increases the response amplitude up to a certain optimal spot size, beyond which further increases in spot size decrease response amplitude. In an on-center ganglion cell (Fig. 1a), a 400- μm spot produced a large, sustained depolarization and a maintained train of action potentials, whereas a 2600- μm spot produced a smaller sustained response that generated only a single action potential at light onset. In the presence of TTX, however, enlarging the spot diameter from 400 to 2600 μm did not decrease the sustained depolarization; this effect was reversed by removing the TTX. This cell responded best to a 400- μm diameter stimulus. In most on-center ganglion cells that we recorded, the optimal spot diameter without TTX was about 400 μm (Fig. 1b). Although TTX had little effect on responses to spots that were smaller than the optimal stimulus diameter, it significantly increased the responses to larger stimuli, and thus reduced these cells' preference for smaller spots. We also encountered a few on-center ganglion cells in which the optimum spot diameter was as small as 100 μm or as large as 800 μm ; the effects of TTX on these cells will be described later.

To verify that the effect of TTX on the receptive-field profile was a network effect and not due to blocking voltage-dependent conductances in the recorded ganglion cell, we did control experiments with electrodes containing QX-314, an intracellular blocker of voltage-dependent sodium currents¹⁹. QX-314 blocked

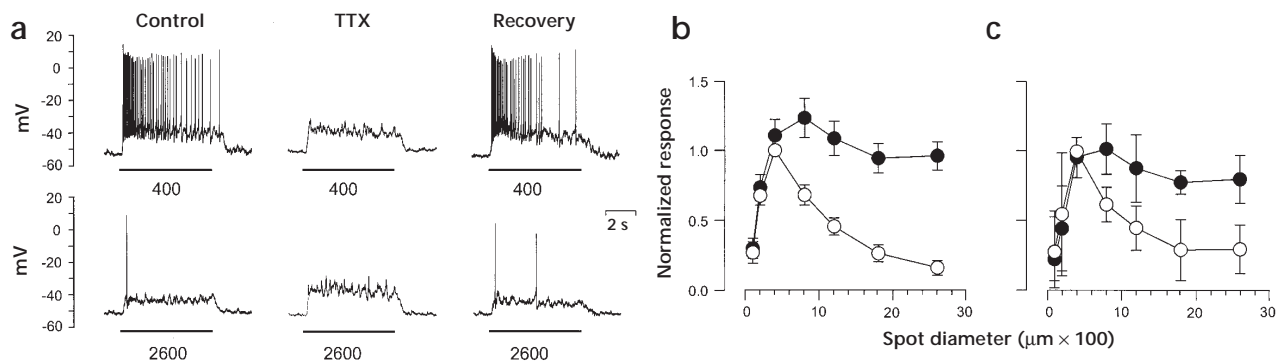


Fig. 1. TTX alters the receptive-field organization of on-center ganglion cells. **(a)** Responses to centered spot stimuli ($8.3 \log$ quanta/cm²/s, or $\log Q$) of $400 \mu\text{m}$ (upper trace) and $2600 \mu\text{m}$ diameter (lower trace) in control Ringer's solution (left), 5 min after addition of 500 nM TTX (middle) and 15 min after washout of TTX (right). **(b)** Response versus spot diameter (receptive-field profile) in control Ringer's solution (\circ) and in 500 nM TTX (\bullet) for on-center ganglion cells ($n = 11$) whose receptive-field centers (optimal spot diameter) were about $400 \mu\text{m}$ diameter. In all plots of receptive-field profiles, responses from each cell were normalized to the maximum for that cell in control Ringer's solution. **(c)** QX-314 ($500 \mu\text{M}$ in recording electrode) does not affect receptive-field profile. Action potentials in the recorded cells ($n = 4$) disappeared within 3–5 min after impalement. Data points show responses in control Ringer's solution (\circ) and after addition of 500 nM TTX to the bath (\bullet). Although action potentials in the recorded cells were blocked, the receptive-field profiles in both normal Ringer's solution and TTX were similar to those obtained without QX-314. In **(b)** and **(c)**, light intensities were $8.3\text{--}9.3 \log Q$. In all figures, error bars indicate standard error.

action potentials in the recorded cells but did not alter the receptive field profile (Fig. 1c), which was the same as measured in other cells with normal electrodes. However, subsequent addition of TTX altered the receptive-field profile as described above. Thus the action of TTX was a network effect that was due to blockade of voltage-dependent sodium currents in neurons other than those recorded.

The effects of TTX on ganglion-cell receptive-field organization most likely occurred in the inner retina because outer retinal neurons do not generate action potentials. Although voltage-dependent sodium channels have been described in isolated horizontal cells^{20,21}, they do not seem to contribute to these cells' hyperpolarizing responses to light²². To rule out a possible direct or indirect effect of TTX on surround antagonism in the outer retina, we tested whether TTX affected the responses of outer retinal neurons under the same conditions used in the experiments on ganglion cells. TTX did not significantly affect the sustained responses of horizontal cells to illumination with an annulus (Fig. 2a) or their receptive-field profile measured with spots of different diameters (Fig. 2b). More importantly, TTX did not reduce surround responses produced by annuli in on-center bipolar cells (Fig. 2c) or alter their receptive-field profiles (Fig. 2d). Thus the effects of TTX on ganglion cell receptive-field organization must have been due to blocking lateral inhibition in the inner retina, presumably mediated by sustained activity in amacrine cells.

What type of amacrine cells mediate the lateral inhibition that is blocked by TTX? The two major inhibitory neurotransmitters used by salamander amacrine cells are GABA and glycine²³. The GABA_A/GABA_C antagonist picrotoxin ($150 \mu\text{M}$) increased the response of on-center ganglion cells at all spot diameters (Fig. 3a). This increase was larger than that caused by TTX because picrotoxin also increased the responses to small-diameter spots, which were not affected by TTX. In the presence of picrotoxin, the subsequent addition of TTX did not further increase response amplitudes (Fig. 3b), indicating that all of the TTX-sensitive inhibition was blocked by picrotoxin and thus mediated by GABA. The TTX-insensitive GABAergic inhibition, which was mainly from nearby illumination, was probably also in the inner retina

because picrotoxin does not block surround antagonism in salamander bipolar cells²⁴. Together, these results suggest that the GABAergic inhibition in the inner retina consists of two components, a TTX-insensitive inhibition from local illumination

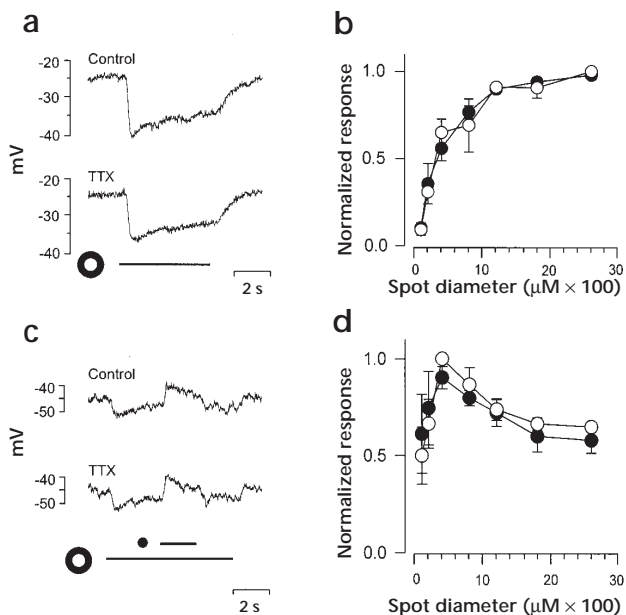


Fig. 2. TTX does not block lateral interactions in outer retina. **(a)** Response of a horizontal cell to an annulus ($500 \mu\text{m}$ i.d., $2600 \mu\text{m}$ o.d., $9.3 \log Q$) in normal Ringer's solution and in 500 nM TTX. **(b)** Receptive-field profile of horizontal cells ($n = 6$) in control Ringer's solution (\circ) and in 500 nM TTX (\bullet). **(c)** Responses of an on-center bipolar cell to an annulus ($1000 \mu\text{m}$ i.d., $2600 \mu\text{m}$ o.d., $9.3 \log Q$), on which was superimposed a centered spot ($400 \mu\text{m}$ diameter, $9.3 \log Q$) in control Ringer's solution and in 500 nM TTX. Horizontal bars below indicate durations of annulus and spot stimuli. **(d)** Receptive-field profile of on-center bipolar cells ($n = 4$) in control Ringer's solution (\circ) and in 500 nM TTX (\bullet).

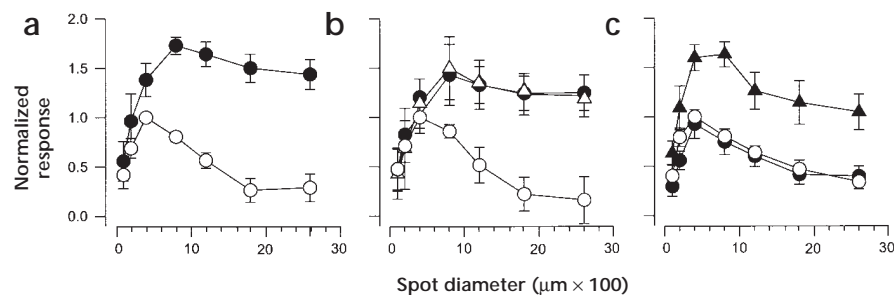


Fig. 3. Effects of picrotoxin and strychnine on receptive-field profiles of on-center ganglion cells. All responses were from cells with receptive-field centers of 400 μm diameter. **(a)** Responses in control Ringer's solution (\circ) and in the presence of 150 μM picrotoxin (\bullet). $n = 6$ cells. **(b)** Responses in control Ringer's solution (\circ), in the presence of 150 μM picrotoxin (\bullet) and after 500 nM TTX had been added while picrotoxin was still present (\triangle). $n = 3$ cells. **(c)** Responses in control Ringer's solution (\circ), in the presence of 2 μM strychnine (\bullet) and after addition of 150 μM picrotoxin while strychnine was still present (\blacktriangle). $n = 5$ cells. Light intensity for all stimuli was near the half-maximal response for a spot of 400 μm diameter (8.3–9.3 log Ω).

and a TTX-sensitive inhibition from more distant sites. However, we could not determine whether these two components were mediated by the same or different GABAergic neurons.

The glycine antagonist strychnine (2 μM) did not affect the sustained responses to spots of any diameter, nor did it prevent the effects of picrotoxin (Fig. 3c) or TTX (data not shown). In the salamander retina, glycine mediates transient lateral inhibition²⁵, a specialized inner retinal mechanism that is activated only by changing or moving stimuli^{3,12–16}. Thus transient lateral inhibition is clearly not involved in the sustained center-surround antagonism that contributes to a ganglion cell's preference for small spots, and so this mechanism did not affect the present results.

Illumination of the surround part of the receptive field can generate a response whose sign is opposite to that produced by illumination of the receptive-field center. If the effect of TTX and picrotoxin on ganglion-cell receptive-field profiles was due to blocking lateral inhibition in the inner retina, then these drugs should also reduce the surround responses elicited by annular stimuli. Illumination of a representative on-center ganglion cell (whose receptive-field profile was similar to those shown in Fig. 1) with an annulus (inner diameter, i.d., 500 μm ; outer diameter, o.d., 2600 μm) that was concentric with the receptive-field center produced a small sustained hyperpolarization in control conditions, but in the presence of TTX, the same stimulus caused a sustained depolarization (Fig. 4). After TTX was washed out, strychnine (2 μM) was applied. The response in strychnine was not different from that in control solution, but after the subsequent addition of picrotoxin (150 μM), the response to the annulus was a sustained depolarization. These results suggest that the annulus stimulated both center and surround mechanisms, and that its stimulation of the center mechanism was revealed when the inner retinal surround mechanism was blocked by TTX or picrotoxin. Because annuli produced a depolarizing (center-like) response when surround antagonism in the inner retina was blocked, we conclude that the outer retinal mechanism contributed relatively little to the hyperpolarization produced by the annulus in control solution. Similar results (reversal of the surround response to a 500 μm i.d. annulus) were found in all of the other on-center ganglion cells tested

with TTX ($n = 8$) and with picrotoxin ($n = 4$). Annuli with a larger (1000 μm) inner diameter caused a smaller surround response that was blocked, but not reversed, by TTX or picrotoxin, presumably because the excitatory (center) mechanism does not extend as far laterally as the inhibitory (surround) mechanism.

In on-center ganglion cells, the hyperpolarizing response to surround illumination is associated with an increase in conductance¹⁸, indicating that at least part of its effect is via direct inhibitory input onto ganglion cells. We tested the ability of TTX and picrotoxin to block this surround-evoked conductance increase. In a representative on-center ganglion cell (Fig. 5), current pulses were passed through the recording electrode using a bridge circuit, which was adjusted so that an increase in conductance produced a positive voltage deflection. An annulus of 1000 μm i.d. elicited a small sustained hyperpolarization that was associated with a large increase in conductance, indicating that it activated a direct inhibitory input onto ganglion cells. The hyperpolarization and associated conductance increase were both blocked by TTX. Conductance measurements could not be made in many experiments because of problems associated with high electrode resistance, but in those cells in which a surround-evoked conductance increase could be measured, it was always blocked by TTX ($n = 5$). The sustained conductance increase evoked by the annulus was not blocked by strychnine but was blocked by the subsequent addition of picrotoxin ($n = 3$).

As noted above, we also recorded from some on-center ganglion cells whose receptive-field center diameters were smaller

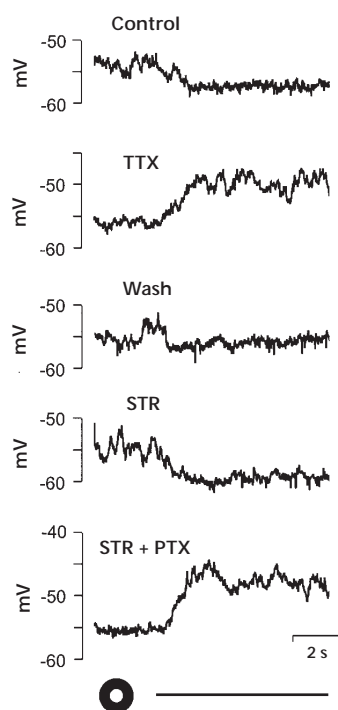


Fig. 4. Effects of TTX, strychnine and picrotoxin on the response of an on-center ganglion cell to surround illumination. Responses of an on-center ganglion cell (receptive-field center diameter, 400 μm) to an annulus (i.d. 500 μm , o.d. 2600 μm , 9.3 log Ω) in control Ringer's solution (control), 500 nM TTX, control Ringer's solution (wash), 2 μM strychnine (STR) and 2 μM strychnine with 150 μM picrotoxin (STR + PTX), in that order. The small variations in resting potential in the different solutions were not significant. Similar effects on the light response were found in other on-center ganglion cells with optimal spot diameters of 400 μm ($n = 15$ for TTX and $n = 8$ for picrotoxin).

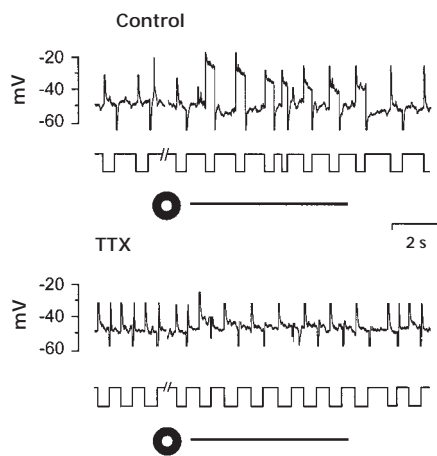


Fig. 5. TTX blocks the conductance increase produced by surround illumination. Responses are from an on-center ganglion cell (receptive-field center diameter 400 μm) in control Ringer's solution and in the presence of 500 nM TTX. Upper trace in each panel is the voltage response of the on-center ganglion cell. Downward deflections of lower trace indicate -0.1 nA current pulses passed through the recording electrode. Light stimulus was an annulus (1000 μm i.d., 2600 μm o.d., 8.3 log Q) of 7-s duration, indicated by the horizontal bar with annulus symbol. The bridge circuit of the amplifier was adjusted to balance out the voltage drop caused by the current pulse in darkness, so that a positive-going voltage drop during the current pulse indicates an increase in conductance. Break in trace before onset of light response indicates 10-s gap when current pulses were not present. In control Ringer's solution, the annulus caused a sustained hyperpolarization and an increase in conductance, both of which were blocked in 500 nM TTX. Stimulus artifacts were eliminated from voltage traces.

or larger than 400 μm . In three groups of on-center cells whose optimal spot sizes in control solution were about 100, 400 and 800 μm diameter, respectively, TTX increased the responses to spots larger than the normal optimal spot size (Fig. 6). However, TTX had a greater effect on cells with smaller receptive-field centers, where it clearly abolished the preference for small spots. TTX had a smaller effect on cells that preferred large spots, and it did not significantly change their already broad spatial tuning. Picrotoxin was also tested on a few of these cells (two with small receptive-field centers and four with large receptive-field centers). In all of these cells, picrotoxin increased the responses to spots of all diameters, and in the cells with small receptive-field centers, it abolished the preference for small spots. Responses to annuli were also measured in the two cells with small receptive-field centers; in both cells, picrotoxin blocked the hyperpolarizing response and the conductance increase produced by the annulus.

Discussion

These results show that the center-surround receptive-field organization of on-center ganglion cells with small receptive-field centers is due mainly to sustained lateral inhibition in the inner retina. This inhibition is mediated by sustained activity in

GABAergic amacrine cells; the lateral propagation of this activity in these cells can be blocked by TTX. Although we cannot rule out the possibility that the action of TTX was indirect, for example, by blocking release of a neurotransmitter or modulator that affected the GABAergic amacrine cells, the simplest interpretation of the results is that voltage-dependent sodium currents are involved in the lateral spread of signals in amacrine cells. In rabbit retina, the lateral spread of signals in amacrine cells with large dendritic fields was reduced when action potentials in those cells were blocked by QX-314 or TTX²⁶. These drugs also reduced the amplitude of EPSPs in the amacrine cells, suggesting that voltage-dependent sodium currents could also amplify EPSPs without generating action potentials. In addition, some amacrine cells in amphibian retinas respond to light with maintained firing of small, TTX-sensitive action potentials²⁷. Although these regenerative potentials are only a few millivolts in amplitude, they might nevertheless provide enough amplification to substantially enhance the lateral spread of signals in these cells.

The TTX- and picrotoxin-sensitive conductance increase produced by annular stimuli in on-center ganglion cells indicates that the inner retinal component of surround antagonism is produced at least in part by GABAergic inhibition directly onto ganglion cells. Our results do not provide any evidence that this inner retinal lateral inhibition also acts on bipolar terminals. However, we should not rule out the possibility that such a presynaptic component exists, because whole-cell patch-clamp recordings in salamander retinal slices have demonstrated synaptically mediated GABAergic input to bipolar cell terminals^{28,29}. These inputs mediate feedback from narrow-field GABAergic amacrine cells and are responsible for generating transient responses in third-order neurons^{11,29,30}. The increased amplitudes of responses to small, centered spots in the presence of picrotoxin may partly result from blocking this local GABAergic feedback to bipolar terminals. Further studies will be necessary to determine if GABAergic inputs to bipolar cell terminals are involved in sustained lateral inhibition.

Although picrotoxin and TTX abolished the preference of ganglion cells for small, centered spots, there was still some suppression of responses to large spots. This suppression is probably due to lateral inhibition in the outer retina, because horizontal cells respond well to large stimuli. However, the ganglion-cell receptive-field profile in picrotoxin may not reflect the exact contribution of lateral inhibition in the outer retina because although picrotoxin does not block surround antagonism in the outer reti-

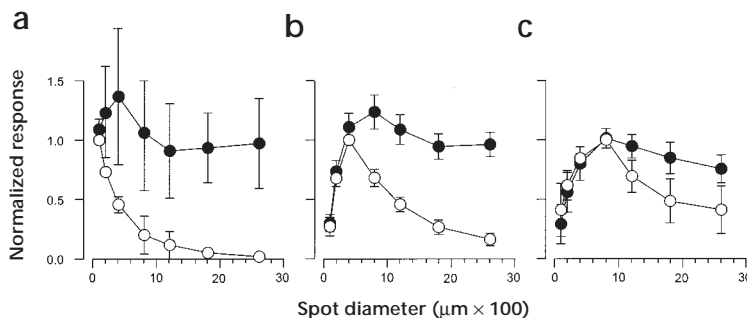


Fig. 6. Effect of TTX on receptive-field profiles of on-center ganglion cells with different receptive-field center sizes. The cells were divided into three groups based on the size of their receptive-field centers (optimal spot diameter), which were 100 μm ($n = 3$) (a), 400 μm ($n = 11$) (b) and 800 μm ($n = 4$) (c). The group with a 400 μm center (from Fig. 1) is included for comparison with the other two. The effect of TTX was strongest on cells with the smallest receptive-field centers.

na in salamander²⁴ or goldfish³¹, it can affect horizontal cell responses. Nevertheless, because TTX, which has no effect on surround antagonism in the outer retina, also abolished the preference for small spots, it is clear that the lateral inhibition in the outer retina has relatively little effect on ganglion-cell receptive-field profiles and imparts at best only a relatively broad spatial tuning to ganglion cells. This might seem strange because lateral inhibition in the outer retina produces strong surround responses in bipolar cells, but the spatial tuning in bipolar cells may be blurred by the convergence of input from many bipolar cells onto a given ganglion cell. The GABAergic lateral inhibition in the inner retina reshapes the spatial tuning in ganglion cells with small receptive-field centers but has less effect on the receptive fields of ganglion cells with large receptive-field centers.

How does lateral inhibition in the inner retina sharpen the spatial tuning in some ganglion cells more than in others? This could be due to selectivity in the inhibitory circuitry, such as differences in inhibitory input to different ganglion cells. Another possibility is that the differences are related to variations in the sizes of ganglion-cell dendritic fields. The size of dendritic trees among on-center ganglion cells in salamander retina shows considerable morphological variation³², but the relationship between dendritic spread and receptive-field center sizes has not been measured. The balance of excitatory and inhibitory inputs to a given ganglion cell might be related to the size of its dendritic tree. Cells with large dendritic fields may integrate both excitatory and inhibitory inputs over a wide area. Cells with smaller dendritic fields may receive excitatory input from a smaller region, but inhibitory input from a wider area could still reach these cells via voltage-dependent sodium current enhancement of lateral conduction in amacrine cell processes. This might explain our observation that TTX only affected responses to spots that were larger than the optimum spot size.

In contrast to our results, blocking action potentials with TTX in rabbit retina did not affect the size of the receptive-field center or block surround responses in ganglion cells²⁶. This is surprising, considering that in the same study TTX blocked the lateral spread of signals in wide-field amacrine cells. However, the ganglion cells tested all had receptive-field center diameters greater than 330 μm . In view of our finding that TTX-sensitive lateral inhibition was most important in ganglion cells with the smallest receptive-field centers, it would be of interest to know if TTX affected the receptive-field center size in rabbit ganglion cells with very small receptive-field centers.

We do not know if the present conclusions also apply to other classes of ganglion cells. Although we recorded from off-center ganglion cells, all of these cells ($n = 14$) had large receptive-field centers that, like those of on-center cells with large receptive-field centers, were not significantly affected by TTX. The role of the inner retinal lateral inhibition in the receptive-field organization of off-center ganglion cells will be more difficult to determine because most of these cells have large receptive-field centers³³, and also because there is more variation in the circuitry underlying their responses^{34–36}. Surround illumination also elicits sustained inhibition in on-off ganglion cells^{37,38}, but the effect of this inhibition on receptive-field profiles is not known. Thus the present conclusions are limited to on-center ganglion cells.

Our results indicate that lateral inhibition in the outer retina contributes relatively little to spatial tuning of ganglion cells. The main function of the lateral inhibition in the outer retina may be to control the gain of synaptic transmission between photoreceptors and bipolar cells¹, via feedback from horizontal cells to cone terminals. Although this confers a center-surround orga-

nization on bipolar cells, it is not sufficient to account for the spatial tuning of all ganglion cells, possibly because of the loss of spatial resolution resulting from the convergence of signals from many bipolar cells onto a single ganglion cell. The GABAergic lateral inhibition in the inner retina is more important for the fine spatial tuning of ganglion cells. We do not yet know whether the GABAergic lateral inhibition in the inner retina can be modulated under different stimulus conditions, and if so, how this is accomplished. The retina offers a unique opportunity to study the mechanisms that control the sizes of receptive-field centers of neurons under different conditions.

Methods

Responses of on-center ganglion cells in superfused eyecup preparations from the tiger salamander (*Ambystoma tigrinum*) were recorded using intracellular micropipettes as described²⁴. Drugs (QX-314 and TTX from Research Biochemicals Inc, picrotoxin and strychnine from Sigma Chemical Co.) were added without substitution to Ringer's solution (110 mM NaCl, 2.5 mM KCl, 1.8 mM CaCl₂, 1.2 mM MgCl₂, 11 mM glucose, 5 mM HEPES, adjusted to pH 7.8 with NaOH). Light stimuli (560 nm) were spots or annuli that were concentric with the receptive-field center, which was determined before each experiment by finding the position at which each of two orthogonal slit stimuli produced maximum responses. Irradiances of the light stimuli (560 nm) at the plane of the retina were measured with a radiometer (UDT555) and are given as log quanta/cm²/s. The sustained response amplitudes used in the plots were averaged over a 1-s period beginning 1s after the onset of the stimulus. All experiments were done under constant conditions of moderate light adaptation with diffuse background illumination (equivalent to 7.5–8.0 log Q at 560 nm), which raised threshold by 1.5 to 2.0 log units relative to fully dark-adapted retinas.

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