Modulation of Sustained and Transient Lateral Inhibitory Mechanisms in the Mudpuppy Retina During Light Adaptation

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Cook, Paul B. and John S. McReynolds. Modulation of sustained and transient lateral inhibitory mechanisms in the mudpuppy retina during light adaptation. J. Neurophysiol. 79: 197–204, 1998. Two functionally and anatomically distinct types of lateral inhibition contribute to the receptive field organization of ganglion cells in the vertebrate retina: sustained lateral inhibition (SLI), which is present during steady illumination and transient lateral inhibition (TLI), evoked by changes in illumination. We studied adaptive changes in these two lateral inhibitory mechanisms in the mudpuppy retina by measuring the responses of on-off ganglion cells to spots of light in the receptive field center, in the absence and presence of a concentric broken annulus (windmill) pattern, which was either stationary or rotating. SLI was measured as the percent suppression of the centered spot response by the stationary windmill and TLI was measured as the additional suppression produced when the windmill was rotating. In dark-adapted retinas SLI was elicited by windmills of 600 or 1,200 μm ID, but TLI could not be elicited by windmills of any size, over a wide range of windmill intensities and rotation rates. Exposure of dark-adapted retinas to diffuse adapting light caused an immediate decrease in the response to the spot alone, followed by slowly developing changes in both SLI and TLI: SLI produced by 1,200 μm ID windmills became weaker, whereas SLI produced by 600 μm ID windmills became stronger. After several minutes strong TLI could be elicited by both 600 and 1,200 μm ID windmills. The changes in SLI and TLI were usually complete within 5 and 15 min, respectively, and recovered to dark-adapted levels slightly more slowly after the adapting light was turned off. However the changes in sensitivity of the spot response were complete within one minute after onset and termination of the adapting light. The adaptive changes in SLI and TLI did not depend on the presence of the adapting light; after a brief (1 min) exposure to the adapting light, the changes in SLI and TLI slowly developed and then decayed back to the dark-adapted level. The effects of the adapting light on SLI were mimicked by dopamine and blocked by D1 dopamine receptor antagonists. However dopamine did not enable TLI in dark-adapted retinas and dopamine antagonists did not prevent enablement of TLI when dark-adapted retinas were exposed to light or disable TLI when applied to light-adapted retinas. The results suggest that light-adaptative changes in SLI are mediated by dopamine and are consistent with a reduction in electrical coupling between neurons that conduct the SLI signal laterally in the retina. In contrast, TLI appears to be switched off or suppressed in the dark-adapted retina and enabled in light-adapted retinas, by a relatively slow modulatory mechanism that does not involve dopamine.

INTRODUCTION

In the retina, light adaptation has been well characterized in terms of changes in response sensitivity and kinetics. However a less well-studied aspect of light adaptation is how adaptive changes in the organization of lateral inhibitory systems contribute to ganglion cell receptive field organization. At least two types of lateral inhibition, sustained lateral inhibition (SLI) and change-sensitive or transient lateral inhibition (TLI), contribute to the receptive field organization of retinal ganglion cells. SLI is present during maintained illumination and is responsible for the well-known center-surround receptive field organization in ganglion cells (Kuffler 1953; Werblin and Dowling 1969). SLI in ganglion cells was considered a consequence of SLI in bipolar cells mediated by horizontal cells in the outer plexiform layer (OPL) (Mangel 1991; Thibos and Werblin 1978a; Werblin 1972). However, there may also be an inner retinal component of SLI (Belgium et al. 1987). TLI, on the other hand, is evoked only by light stimuli that are changing in intensity and/or are moving and is mediated entirely in the inner plexiform layer (IPL), presumably by a class of wide-field, transient (on-off) amacrine cells that make inhibitory synapses onto ganglion cells (Schwartz 1973; Thibos and Werblin 1978a,b; Werblin 1972; Werblin and Copenhagen 1974). Although originally studied in amphibian retina, TLI has also been described in mammals (Enroth-Cugel and Jakiela 1980).

It has long been known that adaptation can affect the receptive field organization of ganglion cells. For example, the increased sensitivity of ganglion cells in the dark-adapted cat retina was associated with an apparent loss of surround inhibition (Barlow et al. 1957; Muller and Dacheux 1997). It is therefore of interest to study how lateral inhibitory mechanisms may be modulated during light and dark adaptation. In theory, changes in lateral inhibitory mechanisms could be the result of switching certain pathways on or off, or by altering their spatial organization, e.g., by changes in electrical coupling between neurons involved in lateral signaling. In this paper we describe changes in both SLI and TLI associated with the process of light adaptation. In mudpuppy ganglion cells, SLI can be elicited in both dark- and light-adapted retinas, but its spatial profile changes with the state of adaptation. In contrast, TLI can be readily elicited in light-adapted retinas but appears to be disabled in dark-adapted retinas. These adaptive changes in SLI and TLI also differ in that the changes in SLI occur more quickly and are mediated by dopamine, whereas the changes in TLI occur more slowly and are not mediated by dopamine.

METHODS

Intracellular recordings were made from ganglion cells in the mudpuppy eyecup preparation (Belgium et al. 1982; Dong and McReynolds 1991). Mudpuppies (Necturus maculosus) were pur-
chased from Kons Scientific (Germantown, WI) and kept in an aquarium on a 12-h light:dark cycle. The care and use of animals was in accordance with the guidelines of the University of Michigan and the Association for Research in Vision and Ophthalmology. Experiments were performed during the daytime. Under dim illumination, animals were decapitated, the eyes were removed, the lens and anterior portion of the eye were dissected away and as much as possible of the vitreous humor was removed with forceps. The eyecup preparation was then placed in a chamber in a light-tight Faraday cage, where it was continuously superfused with amphibian Ringer solution containing (in mM/l) 110 NaCl, 2.5 KCl, 1.8 CaCl₂, 1.2 MgCl₂, 11 glucose, 5 N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) buffer, adjusted to pH 7.8 with NaOH. Except where otherwise noted, all retinas were allowed to dark adapt for at least 1 h before beginning an experiment.

Intracellular recordings were made with ultrafine micropipettes (resistance 300–500 MΩ when filled with 2 M K-acetate) and conventional electronics. Penetration of ganglion cells was sometimes effected by brief overcompensation of the amplifier’s capacitative feedback circuit. ON-OFF ganglion cells were identified by their depth in the retina (almost immediately after touching the retinal surface), transient depolarizations at the onset and offset of the light stimulus, multiple large (>50 mV) action potentials associated with the light-evoked excitatory postsynaptic potentials (EPSPs) and an antagonistic receptive field surround. In mudpuppy retina the only other spiking neurons with transient depolarizations at the onset and offset of a steady light stimulus are transient amacrine cells, in which the EPSPs at light on and light off trigger only one or two large action potentials (Miller and Dacheux 1976; Werblin and Copenhagen 1974; Werblin and Dowling 1969).

Light stimuli were provided by a dual-beam optical system using a 100 W tungsten-halogen lamp. For each beam the stimulus duration and intensity were controlled by electromagnetic shutters and calibrated neutral density filters. All stimuli were 560 nm (a narrowband interference filter was present in the combined, final beam). One beam provided spot stimuli (400 µm diam) and the other beam provided broken annulus (windmill) stimuli (OD 2,600 µm, ID 600 µm) which was either stationary (top) or rotating (bottom). The windmill pattern was either stationary or rotating at 0.25 revolutions/s, which is in the range of rotation rates (0.01 to 0.40 revolutions/s) that produced maximum TLI in mudpuppy ganglion cells (Thibos and Werblin 1978b). Irradiances of all light stimuli after attenuation with neutral density filters were measured at the plane of the retina by using a UDT-555 radiometric detector and are expressed as log Q = log₁₀ quanta cm⁻² s⁻¹. The incident light intensities in log Q can be converted to Rh⁺ (isomerizations photoreceptor⁻¹ s⁻¹). Using the dimensions for mudpuppy rods and cones from Brown et al. (1963) and an axial pigment density of 0.01 µm⁻¹ (Fain and Dowling 1973), the effective collecting areas for mudpuppy rods and cones are ~26 µm² and 7.1 µm², respectively (Eq. 14 from Baylor et al. 1979). Thus Rh⁺ = 26 · 10⁻³ log Q (8) for rods and Rh⁺ = 7.1 · 10⁻³ log Q (8) for cones. For example, the windmill intensity of 8.2 log Q in Fig. 1 is equivalent to 41.5 isomerizations rod⁻¹ s⁻¹. In addition to the test stimuli described above, diffuse background (adapting) illumination was provided by a green LED 5 cm above the eyecup. Because it is difficult to accurately measure the quantal flux of the broadband LED, the intensity of the adapting light was determined, as measured by the responses that it generated in horizontal cells, to be equivalent to 8 log Q at 560 nm. This intensity was found to be sufficient to enable TLI without greatly desensitizing the retina. Because of the considerable time required to test the effects of a given adapting light intensity on all of the parameters tested, only one this adapting light intensity was used in the present experiments.

After a ganglion cell was penetrated and identified, its receptive field center was located by finding the position at which each of two orthogonal slit stimuli (200 × 1,200 µm) produced a maximum response. The dim slit stimuli used for this purpose did not compromise the dark-adapted state of the retina, as evidenced by the fact that ganglion cell responses to dim test spot stimuli were not reduced after the centering procedure. The three stimulus combinations used to measure SLI and TLI (spot alone, spot in presence of stationary windmill, and spot in presence of rotating windmill) were presented in random order at 20 s intervals (or 60 s intervals when the intensity of any test stimulus was >8 log Q). At these intervals the test stimuli themselves did not cause any light-adaptive effects (i.e., the stimuli could be presented repeatedly at this interval with no changes in spot response or effectiveness of stationary or rotating windmills).

Because the responses to dim flashes in dark-adapted retinas were very noisy and because the peak amplitude of the postsynaptic response (EPSP) was often obscured by action potentials, ganglion cell responses were quantified by measuring the area of the EPSP waveform above baseline, after digital filtering using a Gaussian with a ~3 dB rolloff at 10 Hz. This provides a reasonable measure of the response since the number of action potentials was better correlated with EPSP area than with peak amplitude of the EPSP.

RESULTS

Effect of stationary and rotating windmill patterns on ganglion cell responses under different conditions of adaptation

We measured SLI and TLI in ON-OFF ganglion cells of the mudpuppy retina in the manner described by Werblin and colleagues (Thibos and Werblin 1978a,b; Werblin 1972; Werblin and Copenhagen 1974), but in different states of adaptation. SLI was measured as the suppression of the response to a spot in the receptive field center by a stationary windmill (broken annulus) pattern and TLI was measured as the additional suppression produced when the windmill was rotating.

Figure 1 shows the responses of a single ganglion cell to a centered spot (500-ms duration) stimulus under a variety of conditions. For clarity of presentation only the ON-response (EPSP) was often obscured by action potentials, ganglion cell responses to dim test spot stimuli were not reduced after the centering procedure. The three stimulus combinations used to measure SLI and TLI (spot alone, spot in presence of stationary windmill, and spot in presence of rotating windmill) were presented in random order at 20 s intervals (or 60 s intervals when the intensity of any test stimulus was >8 log Q). At these intervals the test stimuli themselves did not cause any light-adaptive effects (i.e., the stimuli could be presented repeatedly at this interval with no changes in spot response or effectiveness of stationary or rotating windmills).
The response-intensity curve in the presence of background light was turned off. For the spot alone the half-saturating intensity was equivalent to 8.0 log unit. The responses recorded when the windmill was rotating were not significantly different from those recorded when the windmill was stationary. Although not shown here, increasing the intensity of the stationary windmill stimulus caused a further shift of the curve to the right, but even with the brighter windmill intensity there was no difference between the effects of the stationary and rotating windmill stimuli.

Figure 2B shows the response-intensity relations measured after the adapting light had been on for 10 min. In the presence of the adapting light the half-saturating intensity for the spot alone was 8.1 log unit. The slope of the curve fit to these responses was slightly less than in the dark-adapted retina, but this was not a consistent result. In the presence of the stationary windmill the response-intensity relation for the centered spot was shifted to the right, but only by ~0.3 log unit. The fact that this shift was less than in the dark-adapted retina indicates that SLI was weaker in the presence of the adapting light. Rotating the windmill caused an additional, downward shift of the response-intensity curve. In other experiments, in which much brighter spot stimuli were used, it was clear that the maximum response was markedly reduced when the windmill was rotating, as described previously (Thibos and Werblin 1978b; Werblin and Copenhagen 1974). In some cells rotation of the windmill also caused a slight shift of the curve to the right, but this variable lateral shift was small relative to the downward shift. Thus in the presence of the adapting light the effects of the stationary and rotating windmill stimuli on the response-intensity curves were essentially the same as described previously by Werblin and colleagues (Thibos and Werblin 1978b; Werblin and Copenhagen 1974).

Figure 2C shows the response-intensity relations for this cell measured during a period 2–10 min after the adapting light was turned off. For the spot alone the half-saturating intensity was again 7.0 log unit, the same as the previous dark-adapted level. The response-intensity curve in the presence of the stationary windmill was difficult to measure during...
windmill persisted for a longer time; 10 min after removal of the background illumination rotating the windmill still caused a downward shift of the response-intensity curve.

**Effect of windmill distance from receptive field center**

The changes in effectiveness of SLI and TLI during and after exposure to an adapting light could be the result of changes in the lateral spread of the signals producing SLI and TLI. Therefore we also measured SLI and TLI using windmill stimuli of smaller inner diameter. Figure 3 compares the suppressive effects of 1,200 and 600 µm ID windmill stimuli in all retinas in which both windmill sizes were tested. The graph indicates the amount of SLI and TLI produced by each type of windmill when retinas were dark adapted (black bars), in the presence of adapting light (white bars) and 3–7 min after the adapting light was turned off (gray bars). SLI was measured as the percent suppression of the spot response in the presence of the stationary windmill and TLI was measured as the additional suppression produced when the windmill was rotating, as described in the legend. In dark-adapted retinas SLI was greater with windmills of 600 µm ID (Fig. 3C) than with windmills of 1,200 µm ID (Fig. 3A), presumably because the windmill stimuli of 600 µm ID illuminated an area closer to the receptive field center. When the retina was exposed to adapting illumination, the SLI produced by windmills of 1,200 µm ID was reduced (Fig. 3A), but the SLI produced by windmills of 600 µm ID was increased (Fig. 3C). In contrast, TLI could not be elicited in dark-adapted retinas with either size windmill but was very strong during and after exposure to the adapting light, regardless of windmill size (Fig. 3, B and D).

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**FIG. 2.** Effects of stationary and rotating windmill stimuli on ganglion cell response-intensity functions under different conditions of adaptation. Responses are from a single cell when retina was dark-adapted (A), in presence of diffuse adapting (background) light (B) and after adapting light was turned off (C). In each section, symbols show average of 2–10 responses to 1-s duration spot stimulus alone (○) and in presence of a 1200 µm ID windmill stimulus that was either stationary (●) or rotating (★). ○, ∗, fit by equation \( R/I_{max} = I/(I + \sigma) \), where \( R \) = response amplitude, \( I \) = spot intensity, and \( \sigma \) = half-saturating spot intensity (Naka and Rushton 1966). For each adaptation state (A–C) values for \( R_{max}, n, \) and \( \sigma \) for best fit to open symbols were determined by using a Marquardt-Levenberg algorithm with unweighted data points. Responses obtained in presence of stationary and rotating windmills were fit by shifting curve laterally (adjusting \( \sigma \)) and/or vertically (by adding a parameter \( S \) to right side of equation). Except for spot and windmill intensities, stimulus parameters in A–C were same as in respective sections of Fig. 1. A: dark-adapted retina. For spot response alone, \( R_{max} = 25.7, \sigma = 7.0, n = 1.1 \). In presence of stationary windmill (7.5 log Q), this curve was shifted to right by 0.6 (\( \sigma = 7.6 \)). Latter curve also fit data obtained when windmill was rotating. B: responses obtained 5–10 min after onset of adapting light. For spot alone, \( R_{max} = 25.2, \sigma = 8.1, n = 0.8 \). In presence of stationary windmill (8.6 log Q) this curve was shifted to right by 0.2 log units (\( \sigma = 8.3 \)). In presence of rotating windmill the latter curve was shifted downward by 0.26 response units (\( S = -0.26 \)) and to right by 0.7 log unit (\( \sigma = 8.7 \)). C: responses obtained during period 2–10 min after adapting light was turned off. For spot alone, \( R_{max} = 25.6, \sigma = 7.0, n = 1.2 \). In presence of stationary windmill (7.5 log Q), this curve was shifted to right by 0.4 log units (\( \sigma = 7.4 \)). In presence of rotating windmill latter curve was shifted downward by 0.49 response units and to right by 0.5 log units (\( \sigma = 7.5, S = -0.49 \)).

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**FIG. 3.** Summary of suppressive effects of distant (1,200 µm ID) and nearby (600 µm ID) windmill stimuli. A: SLI produced by 1,200 µm ID windmills. B: TLI produced by 1,200 µm ID windmills. C: SLI produced by 600 µm ID windmills. D: TLI produced by 600 µm ID windmills. Data are from all cells (\( n = 25 \)) in which standard spot (400 µm diam. 0.5 or 1-s duration) and windmill (600 and 1,200 µm ID, 2,600 µm OD, 0.25 rev/s when rotating) stimuli were used. SLI = \( (R_{stat} - R_{rot})/R_{stat} \) and TLI = \( (R_{stat} - R_{rot})/R_{rot} \), where \( R_{stat} = \) spot response in absence of windmill, \( R_{rot} = \) spot response in presence of stationary windmill and \( R_{wind} = \) spot response in presence of rotating windmill. Measurements were made in dark-adapted retinas (black bars), 10–12 min after onset of adapting light (white bars), and 3–7 min after termination of adapting light (gray bars). Error bars = 1 SE. Spot and windmill stimuli were 8.0–8.4 log Q. For a given cell, spot and windmill stimuli were of equal intensity. * Significance of difference from value obtained in dark-adapted condition, as determined by paired t-tests (\( * P < 0.05; ** P < 0.01 \)). Similar effects of adapting light were seen in 45 other ON-OFF ganglion cells with other spot and windmill sizes, rotation rates, or intensities.
Therefore we tested a wide range of windmill IDs (500 ± 5 m) and rates of rotation (0.04 to 0.6 rev/s). None of these stimuli elicited TLI in dark-adapted retinas, but they all did so after exposure to the adapting light. We also tested the possibility that TLI had an elevated threshold in the dark-adapted retina by increasing windmill intensity by two log units. Because stationary windmill stimuli two log units brighter than the spot completely eliminated the spot response, TLI could not be tested unless the spot intensity was also increased by a similar amount. Under these conditions rotating the bright windmill still failed to cause any additional suppression of the spot response. In the experiment shown in Fig. 4 neither dim (7.7 log Q) nor bright (9.7 log Q) windmill stimuli elicited TLI before exposure to the adapting light, although both of these windmill stimuli elicited TLI after exposure to the adapting light. Thus the inability to elicit TLI in the dark-adapted state is not because TLI has a higher intensity threshold than SLI, because the size or rate of movement of the windmill stimuli necessary to elicit TLI is different in dark-adapted retinas, or because TLI does not spread as far laterally in dark-adapted retinas. It appears rather that TLI is disabled in dark-adapted retinas and enabled in light-adapted retinas.

Time course of changes in SLI and TLI

After the onset and termination of an adapting light, the changes in SLI and TLI occurred much more slowly than did the changes in spot response alone. At the adapting light intensity used in these experiments, the response to the spot stimulus alone decreased to a new steady-state level immediately (within 30 s) after the onset of the adapting light and usually recovered to its dark-adapted value within <1 min after the adapting light was turned off. Although variable, the changes in SLI were usually complete within 2–5 min after the onset of the adapting light and the changes in TLI were complete within 4–10 min. It also appeared that the recovery of SLI and TLI to dark-adapted levels after the termination of the adapting light were somewhat slower than the changes that occurred after onset of the adapting light. It was difficult to measure the time courses of the changes in SLI and TLI more precisely because the test stimuli had to be presented infrequently to insure that the spot and windmill stimuli themselves did not cause any light-adaptive changes (see METHODS).

The fact that after the adapting light was turned off the changes in SLI and TLI persisted long after the spot response itself had recovered to dark-adapted levels makes it unlikely that the mechanism responsible for the decrease in spot response amplitude is also responsible for the changes in SLI and TLI. In fact, the adapting light did not need to be present during the period when the slow light-evoked changes in SLI and TLI were occurring. Figure 5 shows that a relatively brief (1 min) exposure to the adapting light could cause the subsequent slow enablement and decay of TLI in the absence of the adapting light. In this experiment SLI was not measured to increase the time resolution. However other experiments showed that SLI also developed and decayed after a brief exposure to the adapting light, but the time course of these changes was more rapid and thus difficult to measure accurately with the long stimulus intervals used in these experiments.

Effect of dopamine receptor agonists and antagonists on SLI and TLI

The slow time course of the changes in SLI and TLI during and after exposure to adapting light suggests that the modulation of these lateral inhibitory mechanisms by adapting lights may involve neurochemical agents. One likely candidate is dopamine, which mediates several different retinal changes associated with light adaptation (Djamgoz and Wagner 1992; Witkovsky and Dearry 1992).

The effect of dopamine on SLI was similar to that of adapting light. In dark-adapted retinas dopamine (20–100 μM) significantly decreased the SLI produced by windmill intensity of 8.5 log Q.
stimuli of 1,200 μm ID (Fig. 6A) and significantly increased the SLI produced by windmills of 600 μm ID (Fig. 6C). Conversely, in light-adapted retinas the D1 dopamine antagonist SCH23390 (15 μM) significantly enhanced the SLI evoked by windmill stimuli of 1,200 μm ID (Fig. 6A) and significantly decreased the SLI evoked by windmills of 600 μm ID (Fig. 6A). These results are consistent with the idea that the adapting light may affect electrical coupling between neurons mediating the lateral spread of the SLI signal through the retina and that this effect is mediated by dopamine (see DISCUSSION).

Dopamine did not enable TLI in dark-adapted retinas for windmill stimuli of either 1,200 or 600 μm ID (Fig. 6B and D) and SCH23390 did not prevent the enablement of TLI when dark-adapted retinas were subsequently exposed to the adapting light. The possibility that dopamine was necessary but not sufficient for TLI was ruled out by the fact that SCH23390 did not reduce TLI in light-adapted retinas (Fig. 6B and D). In addition, the possibility that dopamine may have an action via D2 receptors is unlikely because the effects of fluphenazine, which blocks both D1 and D2 receptors, were similar to those obtained with SCH23390 (n = 4). The failure of dopamine to enable TLI in dark-adapted retinas and of dopamine antagonists to disable TLI in light-adapted retinas suggests that dopamine is not involved in the enablement and disablement of TLI.

DISCUSSION

The results presented here show that exposure to an adapting light causes significant changes in both sustained and transient lateral inhibition and that these changes persist for some time after the adapting light is removed. The adaptive changes in SLI and TLI are substantively different. In the case of SLI, exposure to adapting light causes a change in its spatial profile, in that the suppressive effects of distant stimuli are reduced whereas those of more nearby stimuli are increased. In contrast, TLI appears to be disabled in the dark-adapted retina and enabled during light adaptation. Furthermore, the changes in SLI and TLI occur with different time courses and only the changes in SLI appear to involve dopamine. These results suggest that quite different mechanisms are involved in the modulation of these two types of lateral inhibition in the retina.

Synaptic pathways involved in SLI and TLI

Figure 7 summarizes the pathways that have been proposed to mediate SLI and TLI in ganglion cells. In this diagram the lateral elements that may mediate SLI are shaded and those that mediate TLI are filled. SLI in ganglion cells is thought to be at least partly a consequence of SLI in bipolar cells, mediated by the lateral spread of signals through horizontal cells in the outer plexiform layer (Mangel 1991; Thibos and Werblin 1978a; Werblin 1972). However a population of sustained amacrine cells is also included since there is evidence for an inner retinal contribution to SLI in ganglion cells (Belgium et al. 1987). This postulated inner retinal contribution to SLI is shown as via a series of laterally connected cells because it has been suggested that the lateral processes of sustained amacrine cells in mud-puppy and salamander retina do not extend very far (Werblin et al. 1988; Yang et al. 1991). On the other hand, the transient amacrine cells that mediate TLI are believed to have processes that extend widely through the IPL (Thibos and Werblin 1978b; Werblin 1972; Werblin and Copenhagen 1974; Werblin et al. 1988; Yang et al. 1991). This diagram includes only those transient and sustained amacrine cells, which are thought to contribute to the lateral spread of SLI and TLI; there may also be other types of sustained and transient amacrine cells, which are not involved in either type of lateral inhibition. For example, the transient re-
sponses of third-order retinal neurons are believed to be generated by delayed negative feedback from GABAergic amacrine cells onto bipolar terminals (Werblin et al. 1988). The amacrine cells that mediate this feedback (not shown) may be different from those that mediate SLI and TLI in the inner retina. For simplicity, the synapses between neurons are not shown. However, the actual connections may be quite complex, because the lateral elements involved in both SLI and TLI may make both feedforward and feedback synapses; horizontal cells may synapse onto bipolar dendrites as well as onto photoreceptor terminals and amacrine cells may synapse onto bipolar terminals as well as onto ganglion cells. The relative contributions of these different pathways to the SLI and TLI observed in ganglion cells is not yet known.

In mudpuppy and tiger salamander ganglion cells TLI is mediated by glycinegenic amacrine cells and spreads laterally via action potentials (P. Cook, P. Lukasiewicz, and J. McReynolds, unpublished manuscript). The pharmacology of SLI is less clear. Although it has been suggested that GABA mediates lateral inhibition in the outer retina (Murakami et al. 1982; Wu 1986), more recent studies suggest that other transmitters may be involved (Burkhardt 1993; Hare and Owen 1996; Verweij et al. 1996). The neurotransmitter(s) mediating the postulated inner retinal component of SLI are not known.

Adaptive changes in SLI and TLI

In light-adapted retinas the effects of stationary and rotating windmill patterns on the ganglion cell response-intensity curves are similar to those reported in earlier studies of SLI and TLI (Thibos and Werblin 1978a,b), except that in the earlier studies rotating the windmill caused only a downward shift of the curve. Our finding that rotating the windmill may shift the response-intensity curve slightly to the right as well as downward suggests that the mechanism of TLI may be more complicated than previously supposed. One possibility is that the amacrine cells that mediate TLI may inhibit bipolar axon terminals as well as ganglion cells. Indeed, glycinegenic input to bipolar axon terminals has been described in tiger salamander (Maple and Wu 1996). In dark-adapted retinas, the stationary windmill shifted the ganglion cell response intensity curve to the right, as in light-adapted retinas, but rotating the windmill had no additional effect, indicating that TLI was not active in dark-adapted retinas.

One might imagine that the inability to elicit TLI in dark-adapted retinas is because TLI is driven only by cones, whose threshold was not reached by the dim windmill stimuli used in the dark-adapted retinas. This is unlikely, however, because even bright (9.7 log Q) windmill stimuli, which were well above threshold for mudpuppy cones (Fain 1975; Fain and Dowling 1973), did not elicit TLI in dark-adapted retinas (cf. Fig. 4), whereas dim (7.5 log Q) windmill stimuli could elicit strong TLI for many minutes after the adapting light was removed. It thus appears that TLI is disabled in dark-adapted retinas by a modulatory mechanism.

The qualitatively different effects of light adaptation on SLI and TLI (a change in the spatial profile of SLI versus enablement/disability of TLI) may be related to differences in the neural architecture of these two systems. As discussed above, SLI is thought to be mediated in the OPL, and perhaps also in the IPL, by a network of neurons connected via gap junctions, whereas TLI is thought to be mediated by neurons with long processes that use action potentials to transmit signals laterally in the IPL. The effects of adapting lights and dopamine on SLI are consistent with the fact that they cause a decrease in electrical coupling between horizontal cells. Because uncoupling horizontal cells will decrease their responses to distant stimuli and increase their responses to nearby stimuli (Dong and McReynolds 1991; Piccolino et al. 1984), such changes could explain why adapting light caused a decrease in the SLI produced by distant windmill stimuli and an increase in the SLI produced by nearby windmill stimuli. Uncoupling a network of sustained amacrine cells might have a similar effect on any component of SLI in the inner retina. The fact that both light adaptation and dopamine strongly reduced SLI produced by distant windmills suggests that if there is an inner retinal component of SLI in mudpuppy then that component is also modulated by adapting lights and dopamine. Although the effects of dopamine and light adaptation on amacrine cell coupling have not been studied in amphibian retinas, both dopamine and light adaptation modulate electrical coupling between all amacrine cells in rabbit retina (Bloomfield et al. 1997; Hampson et al. 1992; Mills and Massey 1995).

Although the present study shows that TLI is disabled in dark-adapted retinas and enabled in light-adapted retinas, further studies will be necessary to determine the mechanism by which these changes occur. Some possibilities to consider are that the transient amacrine cells that mediate TLI are tonically inhibited in dark-adapted retinas or that the enablement and disablement of TLI may involve modulation of the synaptic inputs or outputs of these amacrine cells. If the transient amacrine cells that mediate TLI can be identified, recording from these cells in light- and dark-adapted conditions may provide information about these possibilities. The relatively slow time courses of the enablement and disablement of TLI suggest that this modulation may involve metabolic changes, possibly involving the synthesis of a neuromodulator substance or up- or down-regulation of receptors for such a substance. Certain morphological changes in the inner plexiform layer, for example the formation of spines on bipolar-amacrine synapses in goldfish retina (Behrens and Wagner 1996; Yazuilla and Studholme 1992) are also associated with light and dark adaptation.

What is the functional significance of the adaptive changes in SLI and TLI? In the case of SLI, light adaptation reduces the inhibitory effect of distant surround illumination and increases the inhibitory effect of nearby surround illumination. This spatial “tightening” of steady center-surround antagonism in light-adapted retinas might increase contrast detection at higher spatial frequencies. TLI may be related to motion detection or directional selectivity or possibly “attention” in the sense that a moving stimulus at one location will tend to inhibit ganglion cell firing in other locations. The disablement of this inhibitory mechanism in dark-adapted retinas may also help optimize the detection of dim stimuli.

In conclusion, the present results indicate that light adaptation involves modulation of two functionally distinct types of lateral inhibition that affect the receptive field organiza-
tion of retinal ganglion cells, most likely by different neuro-
modulatory substances. Further studies will be needed to
fully determine the exact circuitry and pharmacology of these
lateral inhibitory mechanisms and their modulation
during light and dark adaptation.

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REFERENCES

BARLOW, H. B., FITZHUGH, R., KUFfLER, S. W. Change of organization in the
receptive fields of the cat’s retina during dark adaptation. J. Physiol.

BAYLOR, D. A., LAMb, T. D., YAU, K.-W. Responses of retinal rods to

BEHRNS, U. AND WAGNER, H.-J. Adaptation-dependent changes of bipolar
cell terminals in fish retina: effects on overall morphology and spinule

BELGUM, J. H., DVORAK, D. R., AND McREYNOLDS, J. S. Sustained synaptic
input to ganglion cells of the mudpuppy retina. J. Physiol. (Lond.) 326:

BELGUM, J. H., DVORAK, D. R., AND McREYNOLDS, J. S. Strychnine blocks
transient but not sustained inhibition in mudpuppy retinal ganglion cells.

BELGUM, J. H., DVORAK, D. R., McREYNOLDS, J. S., AND MIYACHI, E.-I.
Push-pull effect of surround illumination on excitatory and inhibitory
inputs to mudpuppy retinal ganglion cells. J. Physiol. (Lond.) 388:

BLOOMFIELD, S. A., XIN, D. Y., AND OSBORNE, T. Light-induced modulation
of coupling between All amacrine cells in the rabbit retina. Visual Neuro-

BROWN, P. K., GIBBONS, R. I., AND WALSE, G. The visual cells and visual

BURREHART, D. A. Synchrony feedback, depolarization, and color opponency

DIAMOZO, M.B.A. AND WAGNER, H.-J. Localization and function of dopa-

DONG, C.-J. AND McREYNOLDS, J. S. The relationship between light, dopamine
release and horizontal cell coupling in the mudpuppy retina. J.

ENROTH-CUGELL, C. AND JAKELA, H. G. Suppression of cat retinal ganglion

FAIN, G. L. Interactions of rod and cone signals in the mudpuppy retina. J.

FAIN, G. L. AND DOWLING, J. E. Intracellular recordings from single rods

HARE, W. A. AND OWEN, W. G. Receptive field of the retinal bipolar cell:
a pharmacological study in the tiger salamander. J. Neurophysiol. 76:

HAuMPSON, E.C.G.M., VANey, D. I., AND WEILER, R. Dopaminergic modula-
tion of gap junction permeability between amacrine cells in mammalian

KUFfLER, S. W. Discharge patterns and functional organization of mamma-

MANsEL, S. C. Analysis of the horizontal cell contribution to the receptive
field surround of ganglion cells in the rabbit retina. J. Physiol. (Lond.)

MAPLe, B. AND WU, S. M. Glycinergic receptors and synaptic currents at
bipolar cell dendrites and telodendria. J. Physiol. (Lond.). In press.

MILLER, R. F. AND DACHEUX, R. F. Alpha ganglion cells of the rabbit

MURAKAMI, M., SHIMODA, Y., NAKATANI, K., MIYACHI, E.-I., AND WATA-
NABI, S.-I. GABA-mediated negative feedback from horizontal cells to

Naka, K.-I. AND RusHTON, W.A.H. S-potentials from contour units in the

PpICOLINO, M., NEYToN, J., AND GEpRSVENFELD, H. M. Decrease of gap
junction permeability induced by dopamine and cyclic adenosine 3’,5’-
monophosphate in horizontal cells of turtle retina. J. Neurosci. 4:

SCHwARTZ, E. A. Organization of on-off cells in the retina of the turtle. J.

THIBOS, L. N. AND WERBLIN, F. S. The response properties of the steady
antagonistic surround in the mudpuppy retina. J. Physiol. (Lond.) 278:

THIBOS, L. N. AND WERBLIN, F. S. The properties of surround antagonism
erelated by rotating windmill patterns in the mudpuppy retina. J. Physiol.

VERWEIJ, J., KAMERMAN, M., AND SPEKREISE, H. Horizontal cells feed
back to cones by shifting the cone calcium-current activation range.

WERBLIN, F. S. Lateral interactions at inner plexiform layer of a vertebrate

WERBLIN, F. S. AND COPHENAGEN, D. R. Control of retinal sensitivity: III.
Lateral interactions at the inner plexiform layer. J. Gen. Physiol. 63:

WERBLIN, F. S. AND DOWLING, J. E. Organization of the retina of the mud-

WERBLIN, F. S., MAGUIRE, G., LUkASIEWICz, P. D., ELIASOF, S., AND WU,
S. M. Neural interactions mediating the detection of motion in the retina

WITKOVSKY, P. AND DeARRY, A. Functional roles of dopamine in the verte-

WU, S. M. Effects of gamma-aminobutyric acid on cones and bipolar cells

YANG, Y., LUkASIEWICz, P. D., MAGUIRE, G., WERBLIN, F. S., AND YA-
ZULLA, S. Amacrine cells in the tiger salamander retina: morphology,
physiology and neurotransmitter identification. J. Comp. Neurol. 312:

YAZULLA, S. AND STUDHOLME, S. Light-dependent plasticity of the synaptic
terminals of Mb bipolar cells in goldfish retina. J. Comp. Neurol. 320: