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Activation of a D_2 receptor increases electrical coupling between retinal horizontal cells by inhibiting dopamine release

(fish/interplexiform cells)

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ABSTRACT **In the fish retina, interplexiform cells release dopamine onto cone-driven horizontal cells. Dopamine decreases the electrical coupling between horizontal cells by activating adenylate cyclase through dopamine D_1 receptors. Using intracellular recording, we have studied the effect of dopamine D_2 receptor activation on horizontal cell electrical coupling in the intact goldfish retina. Superfusion of the D_2 agonist LY171555 (quinpirole; 0.2–10 μM) increased horizontal cell coupling, as indicated by a decrease in responses to centered spots or slits of light. The length constant of the horizontal cell network increased an average of 31%. Although dopamine (0.5–20 μM) uncoupled horizontal cells, lower concentrations (e.g., 0.2 μM) initially uncoupled and then subsequently increased coupling beyond initial control levels. The coupling effect of LY171555 (10 μM) was blocked completely by prior application of the D_1 agonist SKF 38393 at saturating (20 μM) or nonsaturating (2.5–5.0 μM) doses. Prior treatment of the retinas with 6-hydroxydopamine, which destroyed dopaminergic neurons, eliminated the coupling effect of LY171555 but not the uncoupling effect of SKF 38393. These results suggest that goldfish horizontal cells contain D_1, but not D_2, receptors and that dopamine activation of D_2 autoreceptors on interplexiform cells inhibits dopamine release onto horizontal cells so that the electrical coupling between horizontal cells increases.**

In the central nervous system, dopamine activates at least two types of dopamine receptors, the D_1 and the D_2 types (1). Activation of postsynaptic D_1 and D_2 receptors stimulates and inhibits, respectively, the enzyme adenylate cyclase (1). Activation of presynaptic D_2 receptors, the dopamine autoreceptors, however, inhibits dopamine release (2).

Both D_1 and D_2 receptors are present in the vertebrate retina. D_1 receptors, linked to the stimulation of adenylate cyclase, have been reported in mammalian and nonmammalian retinas (3, 4) and D_2 receptors, linked to the inhibition of adenylate cyclase, have been found on the photoreceptor cells of fish (5). In addition, D_2 autoreceptors that mediate inhibition of dopamine release are found in the rabbit retina (4).

In most retinas, the dopaminergic cells are primarily amacrine cells, except in teleost fish and New World monkeys, where the dopaminergic cells are primarily, if not exclusively, interplexiform cells (6). This latter cell type makes both pre- and postsynaptic contacts with amacrine and bipolar cells but only presynaptic contact with horizontal, bipolar, and/or photoreceptor cells (6–8).

Horizontal cells receive photoreceptor cell input in addition to input from interplexiform cells. Horizontal cells are extensively electrically coupled to each other, so the receptive field size of these cells is relatively large (9). Exogenous dopamine reduces the receptive field size of horizontal cells by uncoupling the electrical gap junctions between them (10–15). Dopamine appears to activate D_1 receptors on the cells so that adenylate cyclase activity is stimulated, resulting in an increase in cAMP levels and electrical uncoupling (11, 15–17). As a result, the responses of horizontal cells to small spots of light increase in size—that is, the size of their receptive fields is decreased. Dopamine application also reduces the response of horizontal cells to diffuse or full-field light stimulation, a phenomenon that is unrelated to horizontal cell coupling (13, 14).

Because adenylate cyclase-linked D_2 receptors are found in the retina (5, 18), we tested whether activation of D_2 receptors with a specific D_2 agonist could affect the electrical coupling and receptive field size of horizontal cells in the fish retina. Our results indicate that, although activation of D_1 receptors uncouples horizontal cells, activation of D_2 receptors couples them. However, prior application of a D_1 agonist or destruction of dopaminergic interplexiform cells by the use of 6-hydroxydopamine (6-OHDA) pretreatment eliminated the coupling action of the D_2 agonist. Our results thus suggest that fish horizontal cells contain D_1, but not D_2, receptors and that dopamine activation of D_2 autoreceptors on the interplexiform cells inhibits dopamine release so that horizontal cell coupling increases.

METHODS

Preparation. Goldfish (*Carassius auratus*), ≈15 cm long, were maintained at 19°C in a 12-hr light/dark cycle. The fish were dark-adapted 20–60 min prior to the start of an experiment, and they were anesthetized with methanesulfonate (MS-222; Sigma). The fish were decapitated and pithed; their eyes were enucleated and their retinas were isolated from the pigment epithelium. These intact retinas were then placed into a Teflon superfusion chamber receptor side up. All procedures were performed under dim red illumination.

The superfusion solution, maintained at ≈20°C, contained 110 mM NaCl, 2.5 mM KCl, 20 mM $NaHCO_3$, 0.1 mM $CaCl_2$, 0.1 mM $MgSO_4$, and 20 mM glucose and flowed by gravity at a rate of 2.0 ml/min into the superfusion chamber. Oxygenation with a mixture of 97% O_2/3% CO_2 maintained the superfusate at pH 7.6 in the retinal chamber. Test drugs were added to the superfusate with a system of two-way stopcocks and manifold. Dopamine solutions contained 0.1 mM ascorbic acid to prevent oxidation. The specific D_1 agonist SKF 38393 and the specific D_2 agonist LY171555 (quinpirole; Research Biochemicals, Natick, MA) were dissolved in dimethyl sulfoxide (DMSO) and diluted in Ringer's solution 100- to 1000-fold before application to the retina. Control experiments indicated that 0.1 mM ascorbic acid or 1%

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Abbreviation: 6-OHDA, 6-hydroxydopamine.

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DMSO had no effect on the light responses or membrane potential of cone horizontal cells.

Some of the fish (n = 7) received a 5-μl injection of 6-OHDA (10 g/liter) containing pargyline (10 g/liter) and ascorbic acid (1 g/liter) dissolved in a NaCl solution (9 g/liter), into one eye on 2 consecutive days 6–14 days before the recording experiments (19). The same volume of the NaCl solution containing ascorbic acid was injected into the other eye as a control. Analysis of the 6-OHDA-treated and the control retinas by high-pressure liquid chromatography with electrochemical detection (20) indicated that 6-OHDA treatment (0.26 ± 0.11 ng of dopamine per mg of protein; n = 6) depleted the retinas of dopamine by an average of 94% compared to saline-injected controls (4.2 ± 0.4 ng of dopamine per mg of protein; n = 7).

Photostimulation, Recording System, and Cell Identification. A dual-beam photostimulator provided two independent light channels so that stimulus intensity, wavelength, and size could be varied. The maximum, unattenuated light intensity of the light channels from a 100-W tungsten/halogen lamp was 5×10^{15} photons·cm^{-2}·sec^{-1} at 500 nm. Calibrated neutral-density filters from log −6.0 to log 0.0 were used to control light intensity, and narrow-band interference filters were used to control stimulus wavelength. In addition, a slit of light (8 × 0.1 mm) was displaced across the retina in 75-μm steps and flashed at each position to measure the receptive field profile of horizontal cells. L-type and C-type cone-driven horizontal cells were identified with spectral and intensity response curves and by response waveform (14).

Standard intracellular recording procedures were used. Intracellular pipettes were filled with 2 M potassium acetate and had resistances between 100 and 200 MΩ.

Data Analysis. The spread of current across the horizontal cell network can be quantified by measuring the length constant. Slit stimuli are displaced across the retina and flashed at regular intervals (see above). The effective length constant, λ, of the horizontal cell receptive field can then be determined by the exponential equation:

$$V_x = V_0 e^{-x/\lambda},$$

where V_0 is the response of the horizontal cell when the slit is at the center of its receptive field (x = 0) and V_x is the response of the horizontal cell to the slit a distance x away from the center of its receptive field. The length constant is the distance at which $V_x = 1/e(V_0)$ (11, 21).

The Wilcoxon two-sample test was used for all statistical comparisons between control and experimental conditions.

RESULTS

Data were obtained from 83 L-type cone-driven horizontal cells in normal, short-term dark-adapted retinas. In addition, data were also obtained from 32 L-type cone horizontal cells in 6-OHDA-treated retinas and from 15 L-type cells in saline-injected, control retinas.

As reported previously, application of dopamine (0.5–20 μM) increased the response of cone horizontal cells to small spots of light and decreased the response of the cells to full-field stimuli (Fig. 1*A*). The increase in the response of the cell to a spot stimulus during dopamine application is indicative of a decrease in electrical coupling between horizontal cells. That is, during uncoupling, less current can flow from an illuminated horizontal cell to others that are not illumi-

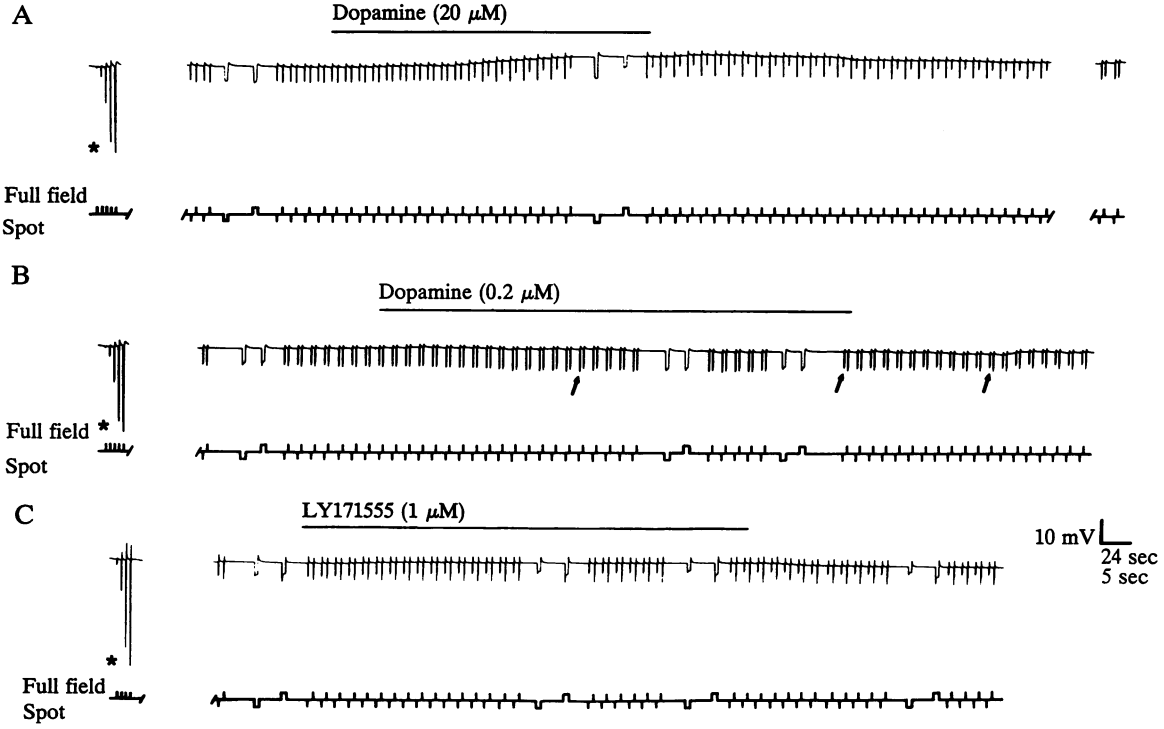

FIG. 1. Effects of dopamine at high (20 μM) or low (0.2 μM) concentrations or of LY171555, a dopamine D_2 receptor agonist, on the responses of cone horizontal cells to spot and full-field light stimuli. Alternately presented spot (diameter, 0.4 mm) and full-field stimuli were initially adjusted in intensity to generate responses of similar amplitude. (*A*) Dopamine (20 μM) increased the response of the cell to the spot stimulus, which is indicative of electrical uncoupling, and decreased the response of the cell to the full-field stimulus, which is indicative of a reduction in light responsivity. (*B*) Dopamine (0.2 μM) initially increased the spot response (indicated by the arrow on the left) but then decreased the same spot response (indicated by the middle arrow and the arrow on the right). That is, after an initial uncoupling, dopamine increased the coupling of the cell to a degree greater than was present during control conditions. (*C*) LY171555 (1 μM) decreased the spot response and increased the response to the full-field stimulus. That is, LY171555 increased the coupling of the cells beyond control values. Asterisks indicate responses to full-field stimuli of increasing intensity.

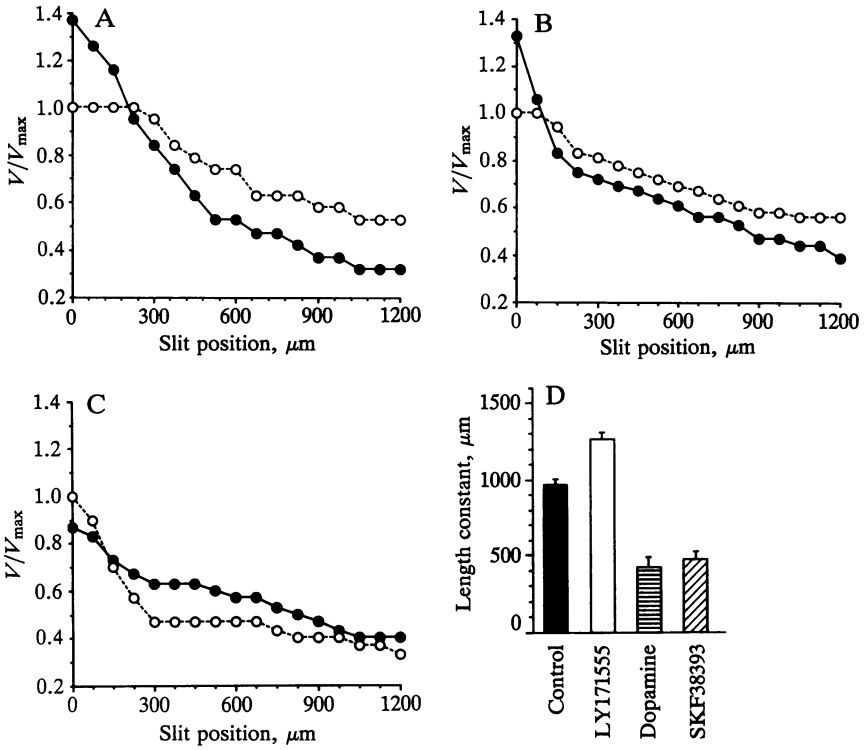

FIG. 2. Effects of dopamine, SKF 38393, or LY171555 on the receptive-field profile of L-type cone horizontal cells and on the length constant of the horizontal cell network. A slit of light (8 × 0.1 mm) was displaced across the retina and flashed at positions 75 μm apart. The amplitude of the horizontal cell response was then plotted as a function of the distance between the slit position at maximum response (the receptive-field center) and every other slit position. Compared to control (○), response amplitude increased more steeply with distance during dopamine (●) (*A*) or SKF 38393 (●) (*B*) application but less steeply with distance during LY171555 (●) (*C*) application. The average length constant decreased during dopamine or SKF 38393 application but increased during LY171555 application compared to control (*D*). All drugs were superfused at 10 μM.

nated and a larger amplitude voltage response is recorded from the illuminated cell. In contrast, changes in response size to full-field stimulation cannot be due to changes in electrical coupling, because with full-field stimulation every horizontal cell receives equal photoreceptor input and there should be little current flow between horizontal cells. Rather, dopamine may decrease horizontal cell responsiveness to light, in addition to uncoupling the cells. Application of a specific dopamine D_1 agonist, SKF 38393 (1–20 μM), also uncoupled horizontal cells and reduced their light responsiveness (see Fig. 3).

Although dopamine applications at concentrations of 0.5 μM or higher produced a sustained uncoupling of horizontal cells, application of dopamine at lower concentrations slightly uncoupled cells initially in a transient fashion and then recoupled them beyond their initial state (Fig. 1*B*).

Although dopamine uncoupled horizontal cells and depolarized them at concentrations of 5 μM or higher (Fig. 1*A*), doses of dopamine between 0.5 and 5 μM uncoupled the cells but produced little effect on their membrane potential (+1.1 ± 0.6 mV; average depolarization ± SEM). Similarly, SKF 38393 (1–5 μM) had little effect on the average horizontal cell potential (+2.0 ± 0.9 mV; see Fig. 3 *B* and *C*).

Because activation of D_2 receptors can inhibit adenylate cyclase activity and can occur at lower dopamine concentrations than activation of D_1 receptors (1), we tested a specific D_2 agonist, LY171555 (quinpirole), on horizontal cell coupling. As shown in Fig. 1*C*, LY171555 (0.1–10 μM) increased the coupling of cone horizontal cells but had little effect on the average horizontal cell potential under these superfusion conditions (+1.5 ± 0.4 mV; see Figs. 1*C* and 3).

Measurements of the receptive-field profile of horizontal cells (see *Methods*) before and during drug applications indicate that the length constant of the horizontal cell network decreases during activation of D_1 receptors and increases during activation of D_2 receptors (Fig. 2). Horizontal cell response amplitude decreases more steeply with distance during dopamine or SKF 38393 application compared with control (Fig. 2 *A* and *B*). In contrast, during application of LY171555, response amplitude decreases less steeply with distance compared with control (Fig. 2*C*). Moreover, the fact that, relative to control, dopamine or SKF 38393 application increased and LY171555 application decreased the slit response at the receptive-field center but that these drugs each had opposite effects on the slit responses at more distant positions indicates that the horizontal cell coupling resistance and not the membrane resistance was primarily affected by these drugs (11). The average length constant of the horizontal cell network, as measured with a slit stimulus (see *Methods*), is reduced ≈50% by dopamine ($P < 0.001$; $n = 7$) or SKF 38393 ($P < 0.002$; $n = 5$) and is increased ≈31% by LY171555 ($P < 0.001$; $n = 10$) compared to control ($n = 20$) (Fig. 2*D*).

Because activation of postsynaptic D_2 receptors has been shown to decrease cAMP levels in the retina (5, 18), it would be possible for the above effect of LY171555 to result from activation of D_2 receptors on the horizontal cell postsynaptic membrane. To test whether goldfish horizontal cells themselves possess D_2 receptors that might directly increase horizontal cell coupling, LY171555 (10 μM) was bath applied after horizontal cell uncoupling by SKF 38393 (2.5–20 μM). This concentration range of SKF 38393 produces a relatively slight (2.5 μM) to a large saturating uncoupling effect (20 μM) (Fig. 3). In every case, however, LY171555 did not affect horizontal cell coupling. These results suggest that D_2 receptors are not on the postsynaptic membrane of horizontal cells but rather are present on dopamine-releasing interplexiform cells.

To test this possibility further, retinas were pretreated with intraocular injections of 6-OHDA (see *Methods*), a procedure that destroys dopaminergic neurons (19). Slit stimuli were used to measure horizontal cell receptive-field profiles from these treated retinas and from control retinas. Prior treatment of the retinas with 6-OHDA eliminated the coupling effect of LY171555 (Fig. 4*B*) but not the uncoupling effect of SKF 38393 (Fig. 4*A*). As shown in Fig. 4*C*, the average horizontal cell length constant was greater in 6-OHDA-treated ($n = 24$) retinas than in saline-injected ($n = 15$) retinas ($P < 0.001$). Moreover, although LY171555 ($n = 5$) application had no effect on the horizontal cell length constant in 6-OHDA-treated retinas ($P > 0.5$), SKF 38393 ($n = 4$) reduced the length constant in these same 6-OHDA retinas ($P < 0.02$). Finally, the average horizontal cell length constant in

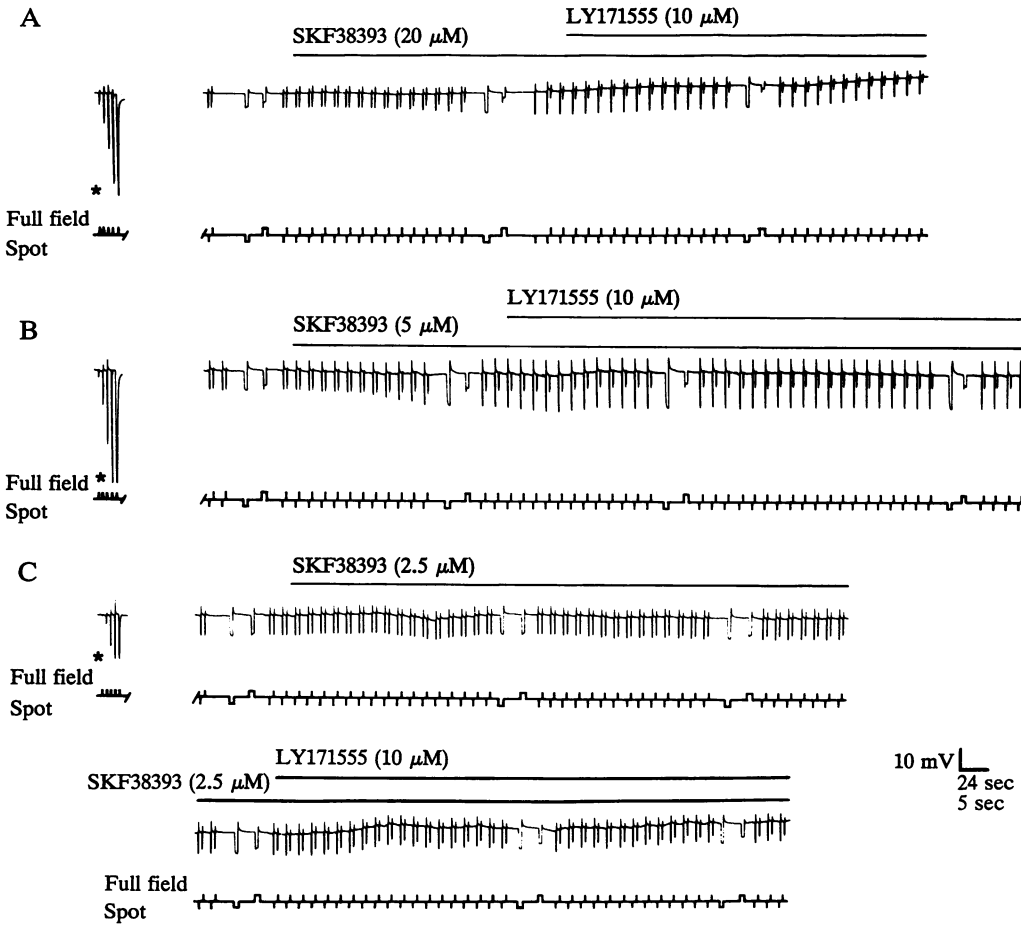

FIG. 3. Prior application of SKF 38393, a dopamine D_1 agonist, blocks the effects of LY171555, a D_2 agonist. Superfusion of SKF 38393 at 20 μM (*A*), 10 μM (*B*), or 2.5 μM (*C*) uncoupled horizontal cells in a dose-dependent manner. Subsequent applications of LY171555 (10 μM) during SKF 38393 superfusion did not affect horizontal cell coupling, even in cases in which the effect of SKF 38393 was below saturation (*C*). This result suggests that LY171555 activates D_2 receptors presynaptic to the horizontal cells.

6-OHDA-treated retinas was similar to the length constant obtained during LY171555 application ($n = 3$) in saline-injected retinas ($P > 0.5$). These results thus suggest that LY171555 couples horizontal cells by activating D_2 autoreceptors on dopaminergic interplexiform cells, thus decreasing dopamine release onto horizontal cells.

DISCUSSION

Evidence of previous studies indicates that dopamine uncouples horizontal cell gap junctions by activation of dopamine receptors on the horizontal cell postsynaptic membrane, because dopamine application uncouples pairs of enzymatically

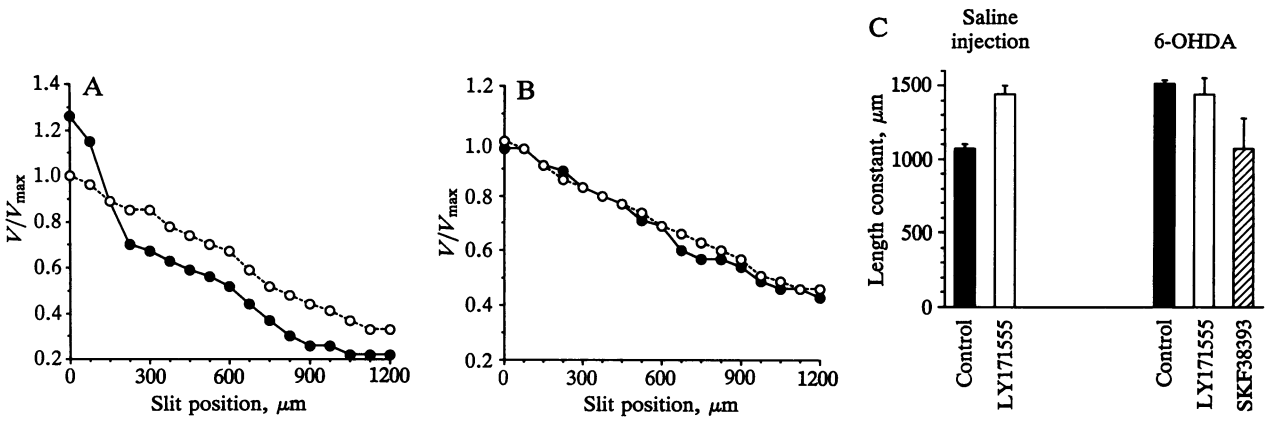

FIG. 4. Effects of SKF 38393 and LY171555 on the receptive-field profile of cone horizontal cells and on the length constant of the horizontal cell network in retinas pretreated with 6-OHDA. Conventions are as in Fig. 2. ○, Control. In dopamine-depleted retinas (6-OHDA pretreatment), SKF 38393 (●) acted just as in normal retinas (*A*; see Fig. 2*B*) but LY171555 (●) was without effect (*B*). Similarly, SKF 38393 decreased the average length constant of the horizontal cell network in 6-OHDA-treated retinas, but LY171555 had no effect (*C*). In saline-injected control retinas, SKF 38393 decreased and LY171555 increased the average length constant of the horizontal cell network, as occurred in normal, untreated retinas (see Fig. 2). These results indicate that depletion of dopamine from the dopamine-releasing cells eliminates the effects of exogenous LY171555 but not of SKF 38393.

isolated horizontal cells (12) and stimulates the activity of adenylate cyclase in isolated horizontal cells (16). Moreover, in Co^{2+}-treated, intact retinas, the dye Lucifer yellow does not diffuse from injected to neighboring horizontal cells after dopamine application (11). These dopamine receptors are of the D_1 type, because D_1, but not D_2, antagonists block the uncoupling effects of exogenous dopamine (11, 15). The findings reported here that dopamine D_1 and D_2 receptor agonists produce opposite effects on horizontal cell electrical coupling and that the coupling effect of a D_2 agonist can be blocked by nonsaturating doses of a D_1 agonist suggests that the postsynaptic horizontal cell membrane contains D_1, but not D_2, receptors. Moreover, because a D_1, but not a D_2, agonist is able to affect horizontal cell coupling in retinas in which 6-OHDA treatment has eliminated presynaptic dopaminergic terminals, it is likely that D_2 autoreceptors are present on interplexiform cells, the principal dopamine-releasing cell of the fish retina. Activation of these autoreceptors by dopamine or D_2 agonists inhibits dopamine release from the interplexiform cells and thus causes horizontal cells to couple more completely. The finding that dopamine increases the coupling of horizontal cells when bath applied in the nanomolar range confirms this suggestion, because D_2, and not D_1, receptors respond to dopamine in the nanomolar range (1).

These data confirm previous suggestions that D_2 autoreceptors are present on dopamine-releasing cells in the vertebrate retina. D_2 agonists inhibit and D_2 antagonists increase calcium-dependent, electrically evoked dopamine release in the rabbit retina (4). Moreover, dopamine synthesis is increased in rat retina by D_2 antagonists (22). Recent evidence also indicates that the mRNA for cloned D_2 receptors is present on cells of the inner nuclear layer (23) so that dopaminergic interplexiform and amacrine cells, in addition to photoreceptors (5, 24), may contain D_2 receptors.

Although our data clearly indicate the presence of D_2 receptors in the fish retina that function as presynaptic autoreceptors, the exact site of these receptors cannot be known with certainty until dopamine release is measured from a fraction of pure interplexiform cell nerve terminals and shown to be inhibited by a D_2 agonist (2). Although it is likely that the D_2 receptors that function as autoreceptors are located on interplexiform cells (4), other sites are possible. For example, if GABAergic amacrine cells had D_2 receptors whose activation stimulated γ-aminobutyric acid (GABA) release, then this would result in an inhibition of dopamine release from interplexiform cells (25). However, two findings argue against the view that dopamine D_2 receptors are located on GABAergic amacrine cells. First, dopamine application inhibits GABA release from the fish retina (26). Second, LY171555 application increases the coupling between fish horizontal cells previously uncoupled by bicuculline (data not shown).

The finding that dopamine, when superfused in the nanomolar range, initially decreases and then subsequently increases horizontal cell electrical coupling (Fig. 1*B*) may indicate that the basal level of extracellular dopamine fluctuates around this concentration (200 nM). In fact, high-speed cyclic voltammetry has indicated that the extracellular dopamine concentration in or adjacent to the subretinal space is $\approx$250 nM (27). During periods of low dopamine release, basal levels of dopamine may tend to remain low and in the nanomolar range due in part to autoreceptor-induced inhibition of dopamine release. This will produce highly coupled horizontal cells. Higher levels of dopamine (micromolar range) during periods of greater release from nearby interplexiform cells will uncouple horizontal cells. This situation would thus accentuate the effect of dopamine on horizontal cell coupling as the dopamine concentration increases from 0.1 to 1.0 μM.

A recent report has indicated that D_2 agonists increase electrical coupling of horizontal cell axon terminals in the turtle retina even in the presence of D_1 antagonists and even after destruction of the dopaminergic cells with 6-OHDA treatment (17). Thus, in contrast to fish, D_2 receptors may be present on the postsynaptic membrane of turtle horizontal cell axon terminals. These results, however, do not rule out the possibility that D_2 autoreceptors may be present on turtle dopamine-releasing cells.

In summary, dopamine-induced effects on horizontal cell electrical coupling in fish are dependent on D_1 receptors on the horizontal cells, which activate adenylate cyclase, and on D_2 autoreceptors on the interplexiform cells, which inhibit dopamine release. Further studies with D_2 agonists and antagonists may elucidate the mechanisms whereby dopamine release is inhibited or stimulated (5, 13, 14, 28).

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