The Effect of Strychnine, Bicuculline, and Picrotoxin on X and Y Cells in the Cat Retina

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ABSTRACT The effect of intravenous strychnine and the GABA antagonists picrotoxin and bicuculline upon the discharge pattern of center-surround-organized cat retinal ganglion cells of X and Y type were studied. Stimuli (mostly scotopic, and some photopic) were selected such that responses from both on and off-center cells were either due to the center, due to the surround, or clearly mixed. Pre-drug control responses were obtained, and their behavior following administration of the antagonists was observed for periods up to several hours. X-cell responses were affected in a consistent manner by strychnine while being unaffected by GABA antagonists. All observed changes following strychnine were consistent with a shift in center-surround balance of X cells in favor of the center. For Y-cell responses to flashing annuli following strychnine, there was either no shift or a relatively small shift in center-surround balance. Compared to X-cell responses to flashing lights, those of Y cells were very little affected by strychnine and in most cases were unaffected. It thus appears that glycine plays a similar role in receptive field organization of X cells as does GABA in Y cells (Kirby and Enroth-Cugell, 1976. *J. Gen. Physiol.* **68:** 465–484).

INTRODUCTION

The effect of intravenously administered bicuculline and picrotoxin upon the behavior of cat retinal ganglion cells was investigated by Kirby and Enroth-Cugell (1976). They observed the discharge pattern to slow square wave stimuli and addressed themselves to the question whether X and Y cells (Enroth-Cugell and Robson, 1966) were affected in the same way by the two agents. Kirby and Enroth-Cugell looked specifically for differential effects upon the center and surround components of the cell's discharge. The conclusion was that in Y cells, but not in X cells, the surround component was substantially reduced whereas the center component was much less decreased in magnitude. The only consistently observed effect of bicuculline and picrotoxin upon X cells was an altered rate of mean firing. These results suggest that gamma-aminobutyric acid (GABA) is a retinal transmitter in the cat, as do the results of Burkhardt (1972) for the frog, Miller and Dacheux (1976) for the mudpuppy, and Caldwell and Daw (1978) for the rabbit.

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This paper deals with further changes in discharge patterns caused by intravenously administered strychnine and bicuculline. It will be shown that X-cell responses are affected in a consistent manner by strychnine while those of Y cells are not.

Because the literature on retinal transmitters is both vast and confusing, and some familiarity with it is required for judging these results, the background is first briefly reviewed.

(*a*) GABA has been widely implicated as a synaptic transmitter in various locations of both vertebrate and invertebrate nervous systems (Roberts et al., 1976), and there is growing evidence that it functions as a neurotransmitter in the vertebrate retina.

Some of this evidence is based on experiments in which the physiological effects of administering GABA were observed. Straschill (1968) and Straschill and Perwein (1969) studied the light evoked activity of cat retinal ganglion cells after intraarterial and iontophoretic administration of GABA. In most, but not all, of their cells the response was decreased. Whether this was because some were X cells, and others were Y cells is not clear since these investigators did not classify their cells. After large intravenous doses of GABA the light-evoked activity of Y, but not X cells is affected (Kirby and Enroth-Cugell, 1976).

GABA is normally present in various vertebrate retinae; Kojima et al. (1958) established this by assaying for GABA in dog and ox. Since then improved techniques have allowed the identification of the specific retinal layers and cell types in which GABA is located, often by assaying for glutamic acid decarboxylase (GAD—the enzyme synthesizing GABA from glutamic acid), GABA-transaminase (GABA-T—the enzyme which metabolizes GABA), or GABA itself.

Autoradiography, demonstrating uptake or exchange of exogenous GABA, has also been used. The retina of several species have been shown to have an active, sodium-dependent, high-affinity uptake system for GABA (Kuriyama et al., 1968; Starr and Voaden, 1972; Tunnicliff et al., 1974; Voaden et al., 1974). All components of the GABA system seem to be concentrated within the inner plexiform layer (Graham, 1974), although there is some scatter throughout the retina (likely due to Muller-cell uptake), and there are also species differences. Recently GABA uptake by a subpopulation of amacrine cells has been demonstrated in the cat (Marshall and Voaden, 1975).

Yet another way of obtaining evidence for a substance functioning as a transmitter is to observe the effects of antagonistic agents, rather than those of the substance itself. This has been done for cat retinal ganglion cells with bicuculline and picrotoxin (Heiss, 1967; Chu, 1968; Kirby and Enroth-Cugell, 1976). These two agents are generally considered to be reliable and specific GABA antagonists, although there are also reports of their lack of specificity (Barker et al., 1975; Starr, 1975). Such cat retinal ganglion cell experiments so far support the idea that GABA is a retinal transmitter.

(*b*) Glycine. The same kinds of experiments as those done to establish GABA's role as a transmitter suggest that glycine also functions as a transmitter in vertebrate retinae.

Glycine administration has been observed to alter the firing of retinal neurons in vitro in the rabbit (Ames and Pollen, 1969) and to inhibit the rabbit electroretinogram (ERG) in vivo (Korol et al., 1975).

Detailed localization of endogenous glycine in the vertebrate retina has not yet been reported; however, there is extensive literature utilizing autoradiography to monitor the exchange or net uptake of exogenous glycine. Such studies in the rabbit (Ehinger and Falck, 1971), pigeon (Marshall and Voaden, 1974), frog (Voaden et al., 1974), and rat, guinea pig, cat, monkey, and human (Brunn and Ehinger, 1974) have shown that radioactive glycine consistently enters cell bodies of the inner nuclear layer and one level

of the inner plexiform layer. It is likely that such uptake occurs for a subpopulation of amacrine cells. High affinity uptake for glycine in those vertebrate retinas where kinetic studies have been performed (Brunn and Ehinger, 1972; Neal et al., 1973; Voaden et al., 1974) are at least consistent with a possible role for glycine as a neurotransmitter. Such uptake systems are sodium-dependent and temperature-sensitive, which suggests a neurotransmitter inactivation mechanism (Curtis and Johnston, 1974; Krnjevic, 1974), which is in turn thought to remove the amino acid from the synaptic cleft and thereby terminate its action. No significant difference has been found between light- and dark-adapted tissue for the total levels of glycine found in the retina (Voaden, 1976). With regard to a possible transmitter role for glycine, an important finding is that there is an increased efflux of radioactive glycine in the light- as compared to the dark-adapted state in both the cat and the rabbit retina (Ehinger and Lindberg, 1974).

Strychnine, presumably a glycine antagonist, affects the discharge of retinal ganglion cells in rabbits (Ames and Pollen, 1969; Wyatt and Daw, 1976) and cats (Chu, 1968; Straschill, 1968). In rats strychnine binds specifically to postsynaptic glycine receptors in the spinal cord (Young and Snyder, 1973). However, other reports on various species claim that strychnine antagonizes acetylcholine (Landau, 1967), B-alanine (Barker et al., 1975), and taurine (Haas and Hosli, 1973; Bonaventure et al., 1974; Barker et al., 1975).

Thus, on the whole the case for glycine as a transmitter in the cat is a good one. It is present in reasonably high concentration and localized to a particular cell type; there is a neural uptake mechanism for it and evidence of release due to light; when applied, glycine itself and its likely antagonist have a definite effect on retinal neurons.

MATERIALS AND METHODS

All experiments were performed on adult cats. Anethesia was induced with either ketamine hydrochloride (20-25 mg/kg intramuscularly) or thiamylal sodium (about 10 mg/kg intravenously), continued during preparatory surgery with thiamylal, and then maintained during the rest of the experiment with intravenous ethyl carbamate (20-30 mg/kg per h preceded by a loading dose of 200-500 mg/kg). Up to 50 mg/kg per h of intravenous gallamine triethiodide was used for muscle paralysis. Mean arterial blood pressure (femoral cannula), expired CO_2, and heart rate were monitored and subscapular temperature was kept at 38°C.

Single unit activity was recorded with lacquer-insulated tungsten electrodes stereotaxically placed in the optic tract. Amplification of the action potentials, which were stored on magnetic tape, was conventional. The cell's discharge in response to 32 full stimulus cycles was averaged and displayed as pulse density tracings (Enroth-Cugell and Robson, 1966).

Response Measure

The magnitude of a response (i.e., the change in firing rate due to light-on in on-center cells and light-off in off-center cells) was obtained in two ways. In some cases, as described in Kirby and Enroth-Cugell (1976; see their Fig. 1), the area bounded by the pulse density tracing and a horizontal line drawn at the level of firing during the end of the preceding appropriate half-cycle (prestimulus-firing rate) was measured with a planimeter and converted to number of impulses. In other cases a computer (PDP 11/10, Digital Equipment Corp., Marlboro, Mass.) calculated the number of spikes occurring within a 100-ms window containing the response peak. Only occasionally did the response peak exceed 100/s, and it was usually considerably below that level.

Stimulators

Two stimulators were used. One had two sources whose stimuli were superimposed by a half-silvered mirror (for details see Kirby and Enroth-Cugell, 1976). Spot stimuli of varying sizes, and annuli of varying inner and outer diameters, from one of the sources could be moved within the receptive field independently of the position of the stimulus from the other source. The optic axis of the stimulator was centered on the receptive field with a mirror. The second stimulator was a three-channel Maxwellian view optical system which provided spot and annulus stimuli of various dimensions and was described in detail by Enroth-Cugell et al. (1977).

Irrespective of stimulator used, stimulus strength was set by adjustment of neutral density in the beam. Either "white" stimuli on "white" backgrounds or green stimuli (Ilford 603) on red backgrounds (Ilford 608, Ilford Ltd., Ilford, Essex, England), were used. All responses were either entirely or predominantly due to the rod system. The equivalent neutral densities of the filters were known from Enroth-Cugell and Shapley (1973) and Enroth-Cugell et al. (1977).

When the Maxwellian stimulator was used, the contact lenses were opaque with a 4.0-4.8-mm clear central pupil. In all cases stimulus luminance was modulated in a square-wave fashion (0.5 – 1.25 s on, same duration off).

X-Y Determination

X-Y diagnosis was often made with a bipartite field, generated by fixed and rotating polarizers, and within which contrast reversed at 2.5 Hz about a constant mean. The dividing line was vertical and the entire field was mounted on a horizontal movement with fine adjustment so that it could be determined whether the cell had a null position or not (Enroth-Cugell and Robson, 1966). Other indicators were also employed (see Kirby and Enroth-Cugell, 1976, p. 468).

Material

Results from 17 cells in 17 cats are presented. 10 cells were X cells, of which 9 were on- and 1 was off-center; 7 cells were Y cells of which 4 were on- and 3 were off-center. Doses of antagonists (strychnine sulfate, Sigma Chemical Co., St. Louis, Mo.; picrotoxin, Sigma Chemical Co., bicuculline, Pierce Chemical Co., Rockford, Ill.) ranged from 0.2 to 0.5 mg/kg body weight.

RESULTS

Antagonists and Receptive Field Organization

Previous results (Kirby and Enroth-Cugell, 1976) showed that X and Y cells are pharmacologically different. The evidence was that intravenously administered picrotoxin and bicuculline, by affecting the center and the surround components of the response differently, strongly shifted the center-surround balance of Y cells (both on- and off-center) while leaving the center-surround balance in X cells unaffected. The primary goal of this study was to observe center-surround balance in X-cells before, during and after administration of strychnine. There was some reduction of the center component but a larger reduction of the surround component of the response in all cases. In general, X cells seemed less affected by strychnine than Y cells by bicuculline and picrotoxin.

RESPONSES TO FLASHING SPOTS IN THE RECEPTIVE FIELD MIDDLE A flashing spot of light smaller than the receptive field center (measured as in Kirby and Enroth-Cugell, 1976) and located in its middle, where the center's sensitivity is

much higher than the surround's, will generate a response which is predominantly due to inputs from the central response mechanism (Stone and Fabian, 1968; Cleland and Enroth-Cugell, 1968). This technique was applied to all but 2 of the 10 X cells using (*a*) strychnine and bicuculline (cells 42-3, 56-2, 74-3); (*b*) bicuculline only (57-1, 70-1, 71-1, 72-4); (*c*) strychnine only (53-4). When both antagonists were used, the second one was administered either when it had become clear that the first had no effect upon the cell's behavior, or when recovery from the first drug was complete. The effect of strychnine on the central response mechanism of two on-center and one off-center Y-cells was also studied. The general experimental procedure in this and the following section was to first obtain a pre-drug averaged control response and then keep all stimulus conditions during and after drug administration unchanged. Recording continued, interrupted only to check eye position, until the unit had either fully recovered from the effect of the drug or was lost.

The results from a strychnine experiment on an on-center X cell (74-3) are shown in Fig. 1. The first antagonist administered was bicuculline but after 42 min there was still no detectable effect and strychnine was injected. Fig. 1 A is the response to a 0.2° spot obtained just before this. Almost immediately, following the administration of 0.4 mg/kg strychnine, there was a slight eye movement. The first reliable histogram was therefore not recorded until 6.5 min after strychnine administration, and after the stimulus spot had been recentered (Fig. 1 B). It was 30% smaller than the control. Finally, histogram C was recorded 30 min after strychnine and recovery was almost complete; to within 4% of the control. Often after strychnine administration there was relatively fast recovery to near the control response, but complete recovery took up to 1.5 h. In the three other X cells tested with strychnine, the reduction of center dominated responses was 18, 21, and 45% respectively. Thus, in those X cells where strychnine was tested, it affected the center mechanism qualitatively in the same manner as GABA antagonists affected Y-cell center mechanisms (Kirby and Enroth-Cugell, 1976). As mentioned above, the GABA antagonist bicuculline had no effect on the center response of the X cell in Fig. 1, nor did it on any of the remaining six X cells which were also tested with bicuculline.

Central responses elicited from Y cells (two on- and one off-center) were essentially unaffected by strychnine administration, except that an increase in prestimulus firing rate (defined in Materials and Methods) occurred. However, the response, as defined in this paper, did not change. From Fig. 1 it is clear that in X cells, too, the prestimulus firing rate changed (compare Fig. 1 A and B) but, in addition, the response decreased.

ADAPTATION OF CENTER AND SUBTRACTION EXPERIMENT The aim of the experiments described in this section was to isolate as well as possible the surround's contribution to the cell's discharge (see Kirby and Enroth-Cugell, 1976, for details), in order to judge the effect of strychnine on the surround mechanism.

Selective Adaptation

It is usually possible to find some combination of area and luminance for a steady-centered adapting spot (i.e., one that remains on continuously) and a

flashing concentric annulus, such that the cell under study is driven largely by its surround. A pure surround response from an on-center cell (see Enroth-Cugell and Pinto, 1972, Fig. 7A) would consist of a sudden decrease in firing rate at annulus *on*, followed by a quite slow recovery towards some new steady level as long as the annulus remains on. As it goes off, the response would

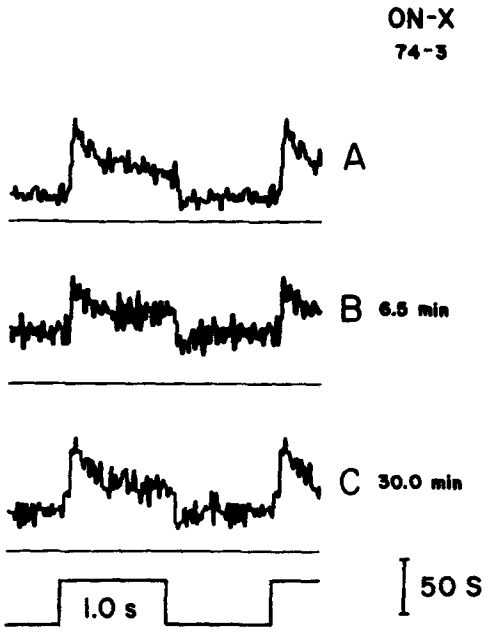

FIGURE 1. Reduction of a center response from an on-center X cell after administration of 0.4 mg/kg strychnine. This cell showed a perfect null-position when the nature of its spatial summation was tested with a bipartite field (Enroth-Cugell and Robson, 1966). (A) Response to a 0.2° flashing spot (0.5 Hz, luminance 3.3×10^{-2} scotopic cd/m^2) in the receptive field middle, obtained before strychnine administration. (B) Response was recorded 6.5 min after strychnine: it showed a 30% reduction, and can be superimposed upon that in A after vertical scaling; i.e. the time-course remained unchanged. (C) Response was recorded 30 min after strychnine and recovery was nearly complete (4% smaller than the control response.) The steady background was 12° in diameter of luminance 1.0×10^{-4} scotopic cd/m^2. The center size (i.e., diameter of equivalent center, D_i; see Cleland et al., 1973, and also p. 468 in Kirby and Enroth-Cugell, 1976) was 2.7°. In this and the next three figures pulse density tracings are averaged for 32 stimulus cycles. The stimulus time-course is given below the response tracing and the thin horizontal line indicates zero impulses per second in this and the three following figures.

consist of a slight overshoot after which firing would be maintained at a level greater than while the annulus was on. In Fig. 2 the stimulus conditions were not optimal for activating the surround alone, since at annulus *on*, the decrease in firing was preceded by a small burst of spikes, there was no slow recovery toward a new steady level, and the increase at annulus *off* was preceded by a

brief dip in firing rate. A pre-drug response to the annulus was obtained (not shown in the figure) and then the first drug, bicuculline, was given. For the next 50 min the mixed averaged response looked precisely as before bicuculline. The response shown in A of the left column of Fig. 2 was obtained at the end of this 50-min period. Shortly after that response had been collected, strychnine was administered and now there was a change in the character of the response; firing frequency was now higher while the annulus was on than while it was off. If this change in firing pattern is interpreted in terms of Rodieck and Stone's

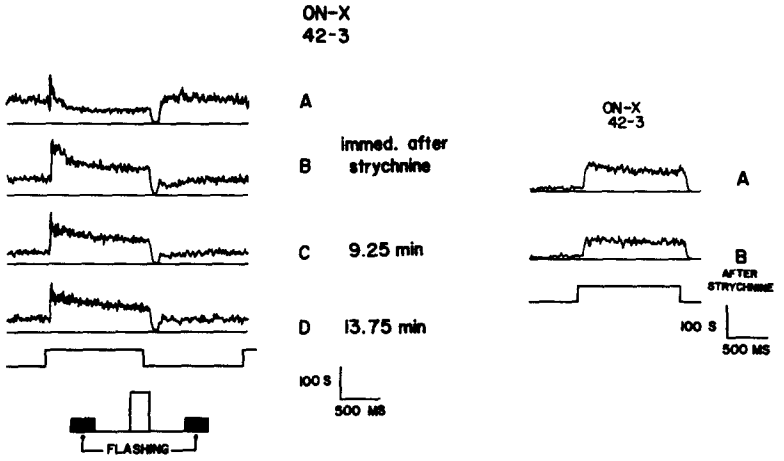

FIGURE 2. Responses from an on-center X cell following administration of 0.4 mg/kg strychnine. Left column: changes in a mixed response. The stimulus (0.4 Hz) was a 3-9.4° flashing annulus (8.0 scotopic cd/m²) and a 1.4° steady adapting spot (30 scotopic cd/m²) centered on the receptive field middle. Zero general background. (A) Response obtained before strychnine was given shows that both the center and the surround contributed to the response. However, after the administration of strychnine (over 2 min) the response (B–D) became strongly center-dominated. A check of eye position revealed no significant eye movement. Right column: reduction of a center response elicited with a 0.4° spot (2.0×10^{-1} scotopic cd/m²) modulated at 0.4 Hz in the receptive field middle. Again there was no general background. The predrug control shown in A was obtained after response A in the left column. B shows the maximum reduction (33%) following strychnine and was obtained immediately after C in the left column. $D_t = 1.7°$.

model for center-surround retinal ganglion cells in the cat (see e.g., Bishop and Rodieck, 1965, p. 120; and Enroth-Cugell and Lennie, 1975, pp. 554–555), it means that there was a shift in the balance of the center and the surround mechanisms in favor of the center. From the experiments described in the previous section, and as shown in the right column of Fig. 2, we know that this same cell's response, due to the center mechanism alone, decreased after strychnine. Hence, the shift in favor of the center seen in the left column of Fig. 2 seems best explained by a substantial decrease in the surround's contribution to the cell's firing paired with a lesser decrease of the center's contribution. In a

second X cell (70-1), bicuculline again left the character of the cell's response quite unchanged for 63 min. At this time strychnine once more initiated a shift in the center-surround balance in favor of the center. However, this effect was not as marked as in the case of the cell in Fig. 2.

When the selective adaptation experiment was repeated on three on- and two off-centered Y cells, the surround component was minimally affected. Fig. 3 shows the results from one of the on-center cells. A 3° steady adapting spot was applied to the receptive field middle and the stimulus was a 8–11° concentric

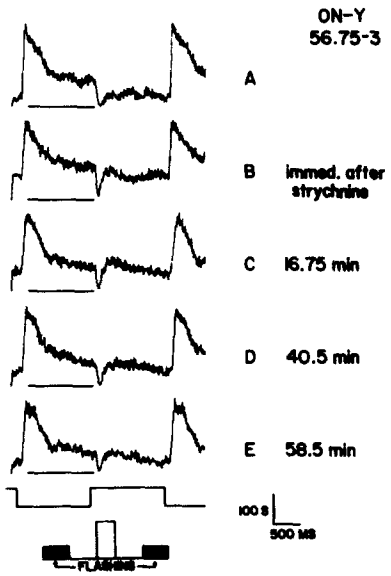

FIGURE 3. Responses from an on-center Y cell following the administration of strychnine. The stimulus (0.4 Hz) was an 8-11° flashing annulus (1.8×10^{-2} scotopic cd/m^2) and a 3° steady adapting spot (5.4 scotopic cd/m^2) centered on the receptive field middle. There was no general background. As shown in the control response A, both center and surround contribute to the response, although it is clearly surround dominated. Response B, recorded immediately after the administration of 0.3 mg/kg strychnine over 2 min, shows some increase in the discharge during "annulus *on*" compared to A. The response is followed for almost 1 h after strychnine (C, D, and E) with little change other than a gradual decrease in the discharge during annulus *on* toward that of the control. $D_t = 2.5°$.

flashing annulus. The pre-drug response is shown in A. Response B was recorded immediately after the administration of 0.3 mg/kg strychnine. The most striking change is an increase in discharge level during annulus *on*. This is still apparent in responses C, D, and E, although the firing frequency is again approaching the control level. Sometimes, as was the case with this cell, a small (5–10%) change was measured in the surround component following strychnine. However, it was always in the opposite direction of that recorded in X cells, or in Y cells following GABA antagonists, i.e., an increase. The only consistent

change in Y cells after strychnine administration was some increase in the prestimulus firing rate.

Before the cell in Fig. 3 was lost, 0.3 mg/kg picrotoxin was administered and the resulting change was identical to that recorded from the X cell in Fig. 2, after strychnine. The firing frequency was decreased while the annulus was off and increased while it was on. This clearly demonstrates the differential effect of strychnine and picrotoxin on Y cells.

Subtraction

Enroth-Cugell and Lennie (1975) subtracted (in a computer) the center response of a cell from the same cell's response when it was driven by both center and surround, thus obtaining an estimate of the surround's contribution to the discharge. (This experiment was described in detail in Kirby and Enroth-Cugell, 1976). In this study the subtraction technique was used to estimate the surround's contribution both before and after administration of strychnine in two X cells (53-4 and 56-2) and two Y cells (41-3, 67-3). The outcome of these experiments confirmed that responses from X cells are unaffected by bicuculline (compare Fig. 9 in Kirby and Enroth-Cugell, 1976), while they are affected by

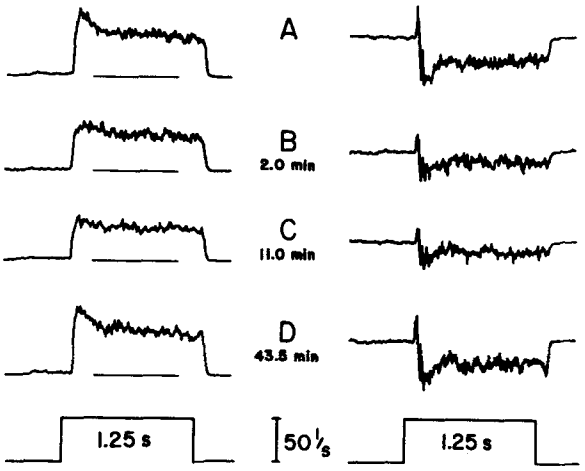

FIGURE 4. Subtraction experiment. On-center X cell. The responses in the left column are predominantly due to the center mechanism (D_t = 2.50, stimulus diameter 2.5°; luminance 1.1 × 10^{-2} scotopic cd/m²; no general background. The right column reflects the behavior of the surround because these recordings are differences obtained by subtracting (in the computer) the response to the 2.5° stimulus from the response to diffuse illumination of the same luminance. Bicuculline was administered first but had no effect on the cell's response. The tracings in A were obtained 47 min after bicuculline and just before strychnine administration. 2 min later, the center component was reduced 15%, the surround component 54%. The maximum reduction is shown for each in C (11.0 min.), 24% for the center and 63% for the surround. Finally in D, 43.5 min after strychnine, both the center and surround components have returned to near control conditions.

strychnine, and that Y cell responses are unaffected by strychnine. Fig. 4 is from an X cell first subjected to administration of bicuculline. 47 min later there was no change whatsoever in the cell's response, so strychnine was administered. As shown in Fig. 4 B, this (within 2 min) resulted in a decrease in both the surround's contribution to the cell's response (obtained by subtraction in the computer) and in the center-dominated response. The maximum decrease of the surround component was more than twice that of the center component (see legend to Fig. 4). Thus, this kind of experiment also indicates that while both the center's and the surround's contribution to an X cell's discharge are reduced by strychnine, the surround suffers the most.

DISCUSSION

These experiments demonstrate the following points: (a) strychnine, a selective antagonist of glycine, affects X-cell responses in the cat retina in a consistent manner. It reduced both the center's and the surround's contribution to the cell's response, but the surround suffers more. This leads to a shift of center-surround balance in favor of the center, which is qualitatively the same kind of effect that GABA antagonists have on Y-cell responses (Kirby and Enroth-Cugell, 1976). (b) Strychnine leaves Y-cell responses unaffected or causes a slight change in the opposite direction to that seen in the X cells. (c) In addition, it was confirmed that bicuculline does not affect the discharge pattern of X cells (Kirby and Enroth-Cugell, 1976). It is not surprising that glycine should be involved in receptive field organization, since, like GABA, it seems to exist in the cat retina in a subpopulation of amacrine cells (Brunn and Ehinger, 1974), and if these are interneurons in the X pathways through the retina (Kolb and Famiglietti, 1974), then interfering with glycine should alter the subsequent response.

It therefore appears that the Y system in the retina utilizes GABA in its information transfer while the X system utilizes glycine. The receptive fields of Y-type ganglion cells somehow use GABA to formulate their message (Kirby and Enroth-Cugell, 1976), which is then passed along to geniculate cells. Although a direct connection of GABA-dependent ganglion cells to GABA-dependent geniculate cells has not been made, it is known that some lateral geniculate nucleus regions of cats are modified by GABA-mediated inhibition (Cameron and Sillito, 1977). It is also known that GABA is released during stimulation of the cat visual cortex (Iversen et al., 1971), and that bicuculline can reverse the cortical effects of deprivation amblyopia in cats (Duffy et al., 1976). While it appears that in the X system the ganglion cell's receptive field depends upon glycine in much the same manner as Y-type ganglion cell receptive fields are dependent upon GABA, the similarity between the two systems certainly breaks down at the cortical level, because as far as is known (Snyder, 1975), glycine does not affect cerebral cortical neurons.

That there was sometimes a slight increase in a surround-dominated response from an X cell after picrotoxin or bicuculline (Kirby and Enroth-Cugell, 1976) and from a Y cell following strychnine is interesting in light of recent reports that there is both GABA-and glycine-dependent input to some ganglion cells in the mudpuppy retina (Miller et al., 1977). The small increase of surround-dominated responses in some cat retinal ganglion cells, following administration

of the antagonist to the nondominant amino acid (strychnine for Y cells and picrotoxin or bicuculline for X cells) may mean that some ganglion cells receive input from both GABA and glycine amacrines. It also seems quite certain that for both X and Y cells some fraction of the centers signal must reach the ganglion cell via amacrines. Unfortunately, a number of possible mechanisms could be suggested on the basis of these extracellular ganglion cell recordings. They provide no evidence whether GABA and glycine are hyper- or depolarizing in the cat retina, or whether they exert their effect on bipolar cells, amacrine cells, or directly on the ganglion cell, and it seems wise to be cautious when drawing comparisons between results obtained on different species. Frumkes and Miller (1978) have suggested from intracellular work on *Necturus* that picrotoxin affects depolarizing bipolars and that strychnine affects hyperpolarizing bipolars. While it would be nice to use their intracellular results to explain these results, the pattern of GABA uptake revealed by autoradiography suggests definite differences between amphibian and mammalian retinae (Voaden, 1976). Caldwell and Daw (1978) have studied the effects of picrotoxin and strychnine on center-surround ganglion cells in the rabbit retina. They reported that while picrotoxin changed the center-surround balance in favor of the center for Y cells but not X cells, strychnine did not effect center-surround balance substantially in either class of cell. Thus, their picrotoxin, but not their strychnine results, agree quite well with those in the cat.

Experiments are currently in progress to determine whether or not systemically administered bicuculline, picrotoxin, and strychnine exert their effect on synaptic regions rather than in some other generalized way on the neuronal membrane itself. It is known that strychnine, bicuculline, and picrotoxin, when added to the medium in which lobster axons are bathed, affect the axons' membrane potential (Freeman, 1973). If this were the case in the cat retina, these results would have to be interpreted in a quite different manner. Preliminary results strongly suggest that picrotoxin and bicuculline are competitive antagonists of synaptic transmission. The strychnine results are suggestive of a noncompetitive type of antagonism, compatible with the results of Snyder (1975). He showed, by examining the influence of a variety of protein modifying reagents on [^{3}H]strychnine binding and its displacement by glycine, that glycine and strychnine might bind to different sites on the glycine receptor.

All the experiments reported in this paper were done in the laboratory of Dr. Christina Enroth-Cugell at Northwestern University, Evanston, Ill. Special thanks are due to Dr. Enroth-Cugell, not only for the generous offer of her laboratory but also for many helpful suggestions on the manuscript. Thanks also to all those in the Evanston "cat lab" for help with the experiments and for reading the manuscript.

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