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Extra-receptive-field motion facilitation in on-off directionally selective ganglion cells of the rabbit retina

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Abstract

The excitatory receptive-field centers of On-Off directionally selective (DS) ganglion cells of the rabbit retina correspond closely to the lateral extent of their dendritic arborizations. Some investigators have hypothesized from this that theories for directional selectivity that entail a lateral spread of excitation from outside the ganglion cell dendritic tree, such as from starburst amacrine cells, are therefore untenable. We show here that significant motion facilitation is conducted from well outside the classical excitatory receptive-field center (and, therefore, dendritic arborization) of On-Off DS ganglion cells for preferred-direction, but not null-direction moving stimuli. These results are consistent with a role in directional selectivity for cells with processes lying beyond the On-Off ganglion cell's excitatory receptive-field center. These results also highlight the fundamental distinction in retinal ganglion cell receptive-field organization between classical excitatory mechanisms and those that facilitate other excitation without producing directly observable excitation by themselves.

Keywords: Retina, Electrophysiology, Ganglion cells, Motion detection, Directional selectivity

Introduction

On-Off directionally selective (DS) ganglion cells of the rabbit retina, like other On-Off center ganglion cells, have a receptive-field (RF) structure that "classically" is considered to consist of an excitatory center region embedded within a "silent", or purely suppressive inhibitory surround. Within the RF center, excitatory responses (increases in firing rate) are elicited at both light onset and offset. Light modulation within the surround is generally thought only to suppress firing evoked by stimulation within the center (Barlow et al., 1964; Barlow & Levick, 1965; Levick, 1967).

The excitatory RF centers of ganglion cells in a number of mammalian species have been shown to be more or less congruent with the extent of their dendritic arborizations; for example, cat alpha and beta cells (Wässle et al., 1981; Peichl & Wässle, 1983), and primate "blue-on," bistratified ganglion cells (Dacey & Lee, 1994). This congruence is particularly precise for On-Off DS ganglion cells of the rabbit retina. In the first reports of their dendritic morphology following intracellular recording, it was shown that differences in the extents of their On- and Off-excitatory RF center regions were reflected in corresponding differences in the inner *vs.* outer sublaminar dendritic arborizations that presumably mediate those responses (Amthor et al., 1984; Amthor et al., 1989).

Recently, it was shown by staining in a visualized, isolated rabbit retina preparation that the excitatory RF center maps and dendritic arborizations of On-Off DS ganglion cells are not only congruent, but about 90% of them are in good register (Yang & Masland, 1992, 1994). These investigators asserted from this finding that because no excitatory responses could be evoked from the region outside the DS ganglion cell's dendritic tree, theories for directional selectivity that postulate a lateral spread of excitation from outside the ganglion cell dendritic tree, such as from starburst (cholinergic) amacrine cells, may be *ipso facto* untenable, because the large dendritic fields of starburst amacrine cells would be expected to conduct excitation laterally from considerable distances outside the ganglion cell dendritic arborization.

In this study, we tested the hypothesis that the role played by laterally extended (amacrine) cells might be primarily to conduct motion facilitation, rather than direct excitation to the On-Off DS ganglion cell. We did this by (1) determining the extent of the excitatory RF center, and therefore dendritic arborization of On-Off DS ganglion cells using small flashing spots; (2) determining whether spots considerably outside the excit-

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atory RF center could facilitate the responses of spots presented inside the center, using an apparent motion protocol; and (3) determining whether this extra-receptive-field-center facilitation was spatially asymmetric along the preferred-null axis. It should be noted that the demonstration of extra-receptive facilitation (requiring an interaction with intra-receptive-field-center excitation to elicit an effect) does not preclude the possibility that some direct, but subthreshold extra-receptive-field excitation may also be conveyed to the RF center from outside it.

The importance of understanding the roles of facilitation *vs.* excitation, and the involvement of possible extra-receptive-field-center mechanisms in the computation of direction of motion in these ganglion cells is a fundamental one. Differential responsivity to opposite directions of motion across the same path occurs in neurons throughout the visual system of vertebrates. Considerable computational modeling of DS mechanisms has been made in species ranging from flies to humans, in central nervous system loci from retina to cortex (see Grzywacz et al., 1994*a*, for a review). On–Off DS ganglion cells of the rabbit retina are a particularly important case for which to resolve this issue, because they exhibit a robust selectivity for direction of motion (Grzywacz et al., 1988, 1990, 1994*a*,1994*b*), and have been particularly well studied physiologically, pharmacologically, and anatomically. Part of the material presented in this paper appeared previously in abstract form (Grzywacz et al., 1993).

Methods

Conventional, single-unit extracellular recordings were obtained from On–Off DS ganglion cells in an isolated retina-eyecup preparation, as described previously (Amthor & Grzywacz, 1991). Adult Dutch belt-pigmented rabbits weighing at least 1.3 kg were anesthetized with an initial dose of urethane (2 g/kg), followed by Pentobarbital given to effect. The amount of Pentobarbital brought the animal to a level of anesthesia in which no reflexive movement or change in heart rate resulted from a pinch to the paw. After anesthesia, the right eye was enucleated as the animal was killed with an overdose of Pentobarbital. The eyecup was then superfused as in the reference above. All surgery and experimental procedures were conducted in rooms illuminated only by very dim, deep red light. Stimuli were presented on a Tektronix 608 CRT monitor, controlled by a Picasso video frame generator, which was in turn controlled by a DOS microcomputer that also recorded the times of occurrence of recorded action potentials. On stimuli were presented against a dark background and Off stimuli were the return to it. The contrast was 99.2% (determined with a Spectra Pritchard photometer model 1980A-WB) and the bright stimulus illumination was 120 lux.

The experimental protocol consisted of three phases. In the first, we determined the preferred direction of the cell and the approximate shape of the excitatory RF center by using hand-controlled stimuli. In the second phase, we determined the RF profile more quantitatively by stimulating the cells with a linear array of 15 60 × 60 μm contiguous spots along the preferred-null axis. The spots (whose centers were 60 μm apart) spanned 900 μm on a line through the middle of the excitatory RF center, as illustrated schematically in Fig. 1A. The response profile was determined by extracellularly recording the light onset and offset responses to a minimum of 30 repetitions of each of these 15 spots, which were presented in a pseudorandom sequence.

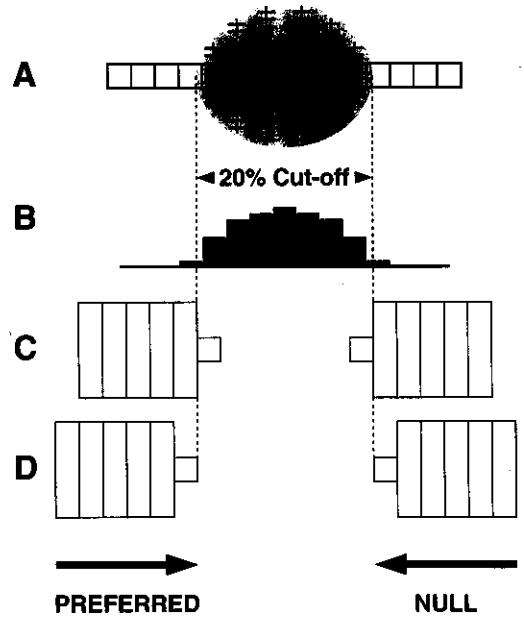

Fig. 1. Schematic illustration of the protocols used in the experiment. A: Illustration of the extent of excitatory RF center defined by excitatory response elicited at the onset (+) and offset (−) of small flashing spots (plus/minus combined symbols; spot size corresponds approximately to symbol size). The excitatory RF center determined by this method, indicated by the shaded area, has been shown to correspond closely to the extent of the cell's dendritic arborization. Superimposed on this excitatory RF center, and extending beyond it, is a linear array of 15 spots used to assess quantitatively the sensitivity profile of the excitatory RF center. B: Schematic response profile obtained after averaging 30 stimulus presentations of each spot position. The 20% cutoff boundary is estimated by linear interpolation. C: Positions of apparent motion stimuli for determining the effect of extra-receptive-field-center slits on responses to spots just inside the 20% cutoff boundary for the excitatory RF center. D: Positions of apparent motion stimuli for determining the effect of extra-receptive-field-center slits on responses to spots just outside the 20% cutoff boundary for the excitatory RF center.

A plot of a "typical" profile obtained at each of the spot positions (averaged combined onset and offset responses) is shown schematically in Fig. 1B. The limits of the excitatory RF center along this line were estimated by linear interpolation as the positions where the responses became less than 20% of the maximum obtained in the middle of the RF. These boundaries are indicated schematically by the vertical dashed lines in Fig. 1B. This 20% contour definition provides a reasonable estimate of the extent of the dendritic field (as demonstrated by Yang & Masland, 1992, using the identical criteria). The steep decline in excitability beyond this 20% point is due to the very strong inhibitory surround of these cells (Barlow et al., 1964; Barlow & Levick, 1965; Levick, 1967).

The third phase of the experiment used the protocol illustrated in Figs. 1C and 1D. We picked four locations for small (60 × 60 μm) spots, two of which were just inside, and two just outside the 20% borders determined above, and six to ten locations for slits 60 μm wide and 400 μm long, placed at 60-μm intervals from just outside the excitatory RF center border to considerably outside the excitatory RF center in the surround.

The scheme for apparent motions towards the spots just inside the excitatory RF center border is shown in Fig. 1C (preferred-direction apparent motion on the left, null-direction apparent motion on the right); that for apparent motion towards spots placed just outside the excitatory RF center border is shown in Fig. 1D. The apparent motion protocol was used to determine if apparent motion stimulation involving any of the slits outside the excitatory RF center could facilitate (or inhibit) the responses to either of the spots just inside or just outside the excitatory RF center.

The apparent motion protocol involved both On and Off modulation of each of the slits 200 ms prior to similar modulation of one of the spots. The onset of the slit occurred 200 ms before the onset of the spot, and likewise, the offset of the slit occurred 200 ms before offset of the spot, so that On–On and Off–Off interaction effects could be segregated from On–Off interactions. (The slits remained on for 1 s, and the delay between the beginning of two consecutive On stimuli was 2250 ms.) This protocol was based on previous findings within the RF center of these cells that facilitatory and inhibitory effects tend to be segregated between On and Off pathways, and that using a 200-ms delay, both facilitatory and inhibitory apparent motion effects could be observed (Amthor & Grzywacz, 1993; Grzywacz & Amthor, 1993).

The strength of facilitation and inhibition was determined by comparing the response of the spots by themselves to the responses obtained when their modulations were preceded by modulations of one of the slits located in the surround. In a few cases, where small excitatory responses were elicited from the slits in the surround (mainly for the slits closest to the excitatory RF center), the method of "base subtraction" described previously (Amthor & Grzywacz, 1991) was used to compensate for the expected small excitatory response due to the slit occurring during, and therefore contributing to, the spot response histogram. For the vast majority of slit presentations base subtraction had little or no effect on the results, because rarely was there any response elicited by slits in the surround, consistent with previous findings cited in the Introduction.

Results

We completed our experimental protocol on a total of 24 cells. All were located within 1 to 2 mm of the visual streak of the rabbit retina, and had RF sizes ranging from 200 to 300 μm. Fig. 2 shows the peristimulus-time (PST) histograms of the responses obtained in the experimental protocol shown in Fig. 1C for an On–Off DS ganglion cell (E525C7), plotted here with the orientation of the preferred direction shown as downward. The results presented for this cell are generally typical for the sample of 24 cells, except where noted. The top and bottom most histograms in Fig. 2 are the extracellularly recorded responses to slits "X" and "Y", respectively, whose centers were 150 μm outside the nearest excitatory RF center border. The modulation of slit X in the surround on the "preferred side" (from which preferred-direction-moving spots approach the RF center) elicited no response whatsoever, as was generally the rule. Mod-

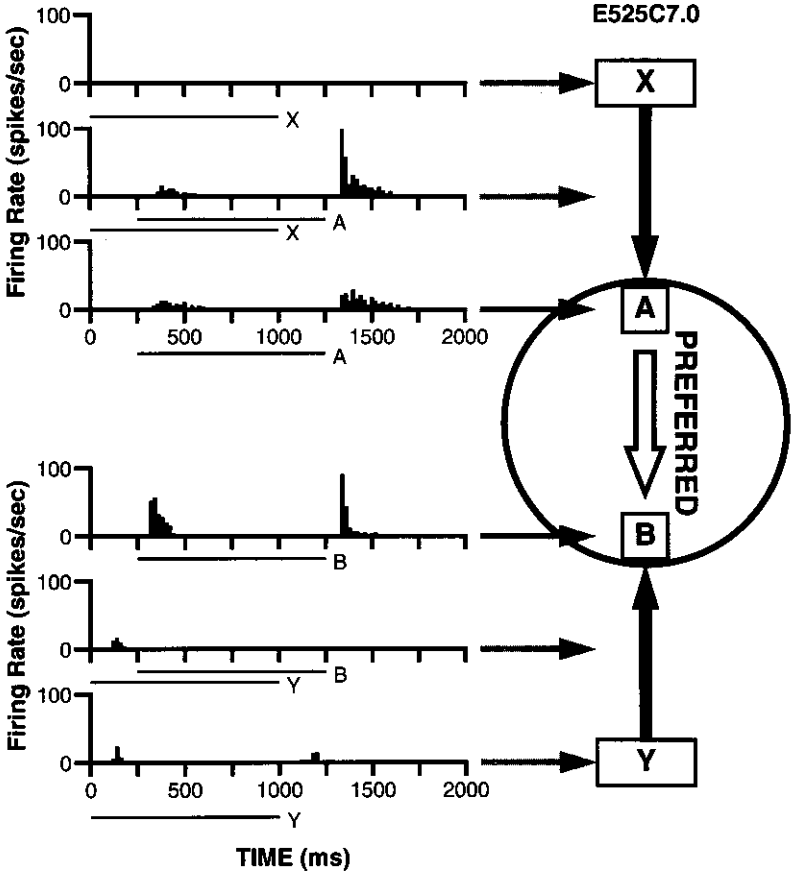

Fig. 2. The PST histograms of the responses obtained in experimental protocol 1C for On–Off DS ganglion cell E525C7. The top most and bottom most histograms are the responses elicited by the slits X and Y whose centers were 150 μm outside the RF center borders. The third and fourth histograms are the responses elicited by the two spots (A and B) just inside the RF center borders. The second and fifth histograms are the responses to the preferred- and null-direction apparent motions (respectively) from the slits towards the spots (indicated by the arrows: X to A is preferred-direction apparent motion, Y to B null-direction apparent motion). Lines underneath the histograms followed by letters A, B, X, or Y give the duration of the stimulus above background. Bin size in this and all other histograms was 20 ms. Histograms are the averages of 50 trials.

ulation of slit Y on the "null side" (from which null-direction-moving spots approach the RF center) elicited a very small response (surround stimulations generally produced little or no responses by themselves).

The third and fourth histograms in Fig. 2 are the responses elicited by spots A and B, which are just inside the top and bottom excitatory RF center borders, respectively. Both spots elicit significant Off responses; the On response of spot A, while significant, is smaller than that of spot B. Small differences in the extent and relative sensitivity of the On- *vs.* Off-center excitatory RF areas are not unusual, and have been previously well documented, as discussed in the Introduction.

The second histogram in Fig. 2 is the preferred-direction apparent-motion response from slit X towards spot A (motion indicated by the heavy, dark, downward-pointing arrow). This histogram shows that the preferred-direction apparent motion increases the spot A offset response significantly (approximately by a factor of 1.8) and the spot A onset response to a somewhat lesser extent. Thus, modulation of a slit located in the surround of a considerable distance from the border of the excitatory RF center, which itself elicits no response whatsoever (top histogram), can facilitate the On and Off responses elicited by a spot within the excitatory RF center. This demonstrates that the facilitatory receptive field extends significantly outside the traditional excitatory RF center.

We used an identical, mirror-image null-direction apparent motion protocol from the surround to the null side of the excitatory RF center border, to determine whether extra-RF-motion facilitation was spatially asymmetric. The fifth histogram shows the response to the null-direction apparent motion (indicated by the dark, heavy, upward-pointing arrow) from the slit Y, outside the RF center, towards the spot B, just inside the RF center. In contrast to the result obtained for the preferred-direction apparent motion (second histogram), the null-direction apparent motion dramatically reduced the spot B onset and offset responses (comparing histogram 5 with histogram 4), despite the fact that a small excitatory response was actually elicited by slit Y in the surround, when presented by itself.

The asymmetry of the motion facilitation effect suggests that the facilitatory RF is direction-of-motion specific, and thus, likely to involve a mechanism distinct from that which mediates the stationary, excitatory RF center that is coincident with the dendritic arborization. However, it should be kept in mind that the protocols reported here can only show that the facilitation observed is *effectively* direction-of-motion specific, and that it could arise either from a truly asymmetric facilitatory mechanism, or a symmetrical mechanism interacting with an asymmetrical inhibitory one.

Fig. 3 shows the average responses (total spikes) elicited by each of the 60 μm × 60 μm spots in the linear array experiment (dashed lines) and for the apparent motions from all of the slits toward the spots just inside the excitatory RF center borders (as shown schematically in Fig. 1C). Fig. 3A (top) shows the results for the Off responses of cell E525C7 (same cell as Fig. 2); Fig. 3B (bottom) shows the results for the On responses of another On–Off DS ganglion cell (E523C2). The responses elicited along the linear array of spots (dashed lines) declines abruptly past the 20% cutoff loci, as reported earlier by Yang and Masland (1992), who showed that the excitatory RF center borders of these cells are similar in size and extent to the underlying On–Off DS ganglion cell dendritic trees. The excitatory RF center diameters for these two cells (which were within 1 mm

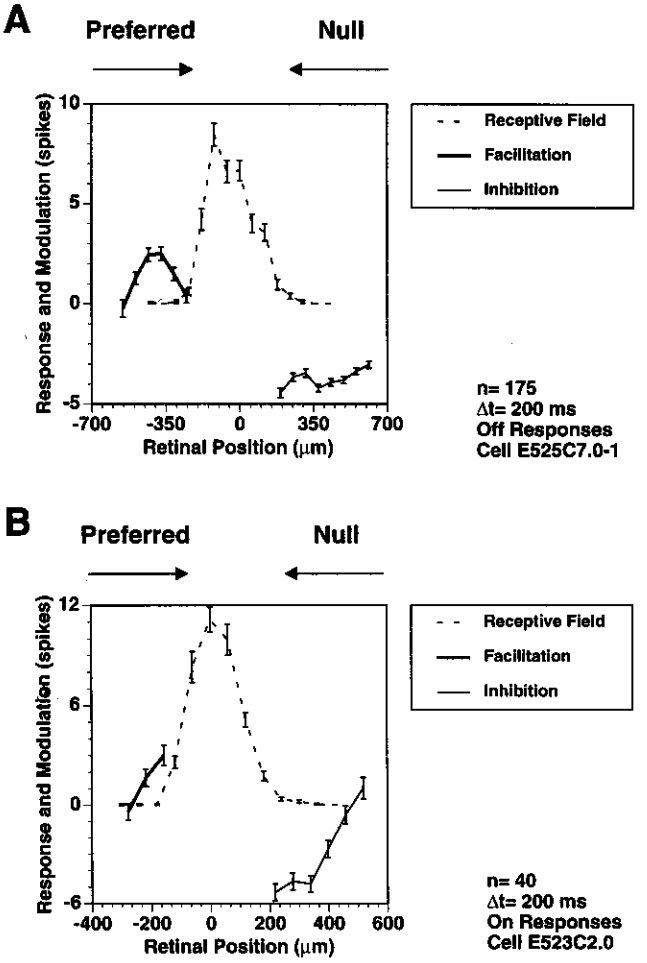

Fig. 3. Extra-receptive-field facilitation and inhibition elicited by apparent motion. The dashed lines show the average responses (number of spikes) for each of the 60 μm × 60 μm spots in the linear array experiment (shown schematically in Figs. 1A and 1B). The solid lines show the changes in the responses to the spots during the apparent motions from each of the slits toward the spots just inside the excitatory RF center borders (as shown schematically in Fig. 1C). The heavy solid lines on the left sides of A and B show the extra number of spikes the apparent-motion facilitatory process elicited as a function of distance (at each slit position). The lighter solid lines on the right sides of A and B show the reduction in the spikes elicited by the spots due to modulation of the slits at various distances on the null side of the excitatory RF center border. The error bars represent standard errors. A: The Off responses of On–Off DS ganglion cell E525C7 (175 trials). B: The On responses of On–Off DS ganglion cell E523C2 (40 trials). In both cells the facilitation effect on the "preferred side" declined to become marginally significant inhibition at the farthest distance shown. At farther distances on the preferred side (not shown), surround stimulation typically produced surround-like inhibition, similar to that observed on the "null side".

of the visual streak) were on the order of 300 μm; those of all 24 On–Off DS ganglion cells recorded within 1 to 2 mm of the visual streak ranged from 200 to 300 μm.

The heavy solid lines on the left side of Figs. 3A and 3B show, as a function of position, the extra number of spikes by which the apparent-motion facilitatory process from each of the slit positions incremented the response to spot A. The results in

Fig. 3A demonstrate that facilitation can be propagated to the RF center from distances as much as 300 μm outside the closest edge of the excitatory RF center. The lighter solid lines on the right side of Figs. 3A and 3B show, as a function of position, the number of spikes by which the inhibitory process (on the opposite side of the RF center) decremented the center excitatory response. The range of inhibition is longer than that of facilitation, and generally exceeded that of the farthest inhibiting slit used in these experiments.

We observed significant extra-RF-center facilitation in fifteen of twenty four cells. For all cells, the facilitation effect elicited by stimuli within the surround declined with distance. At very large distances (beyond that shown in Fig. 3), stimulation within the surround typically became inhibitory, presumably reflecting the normal surround inhibitory mechanism of the cells, which is masked by strong facilitation only at short distances. For the On responses of cell E523C2 (Fig. 3B), facilitation was maximal at the shortest distance tested (30 μm; center of 60 μm wide slit), and was significant out to about 90 μm. For the Off responses of E525C7 (Fig. 3A), the facilitation was not maximal, or even significant, at 30 μm, the shortest distance tested. Instead, the maximum occurred at 150 μm, and facilitation was significant out to 270 μm. The occasional finding of an optimal distance to elicit facilitation is further evidence that it is direction-of-motion specific, and not due to a general summation of the responses to the spot and slit, or to an error in locating the border of the exact excitatory RF center border. In the latter case, the strongest facilitation effect would always be expected to be produced by slits closest to the excitatory RF center, where the greatest excitation would be expected.

The inhibition elicited by the null-direction apparent motion from the surround tended to be strongest for the shortest distances, but its range typically exceeded 300 μm. This result is consistent with previous findings within the RF center of these cells (Amthor & Grzywacz, 1993; Grzywacz & Amthor, 1993) that the spatial range of null-direction inhibition is larger than that of preferred-direction facilitation. It is also consistent with previous results that null-direction inhibition is mediated by a separate mechanism from that of surround inhibition, having distinct timing and spatial range properties; normal surround inhibition is more transient than null-direction inhibition (Amthor & Grzywacz, 1993; Merwine et al., 1995) and thus has a relatively weak effect at the 200-ms delay used in our protocols. As the first stimulus (the slit) in the null-direction apparent motion protocol is placed farther outside the RF center, the specific null-direction inhibitory mechanism declines in strength, and inhibitory effects observed appear to be more dominated by the normal inhibitory surround.

The population statistics for the spatial parameters of preferred-direction facilitation, obtained with the protocol of Fig. 1C, are shown in Fig. 4 for the 24 cells of this study. Fig. 4A shows the percentage of cells having maximal facilitation at particular distances from the excitatory RF center border. As seen for the Off response of cell E525C7 (Fig. 3A), the maximum facilitation distance for many cells was not always the position of the closest slit, suggesting, as discussed above, that the facilitatory effect was truly motion specific.

Fig. 4B shows the percent of cells in which facilitation could be elicited at various distances. In nine of 24 cells, we observed no statistically significant facilitation at any distance outside the RF center (see Discussion). In the other 15 cells, the spatial range of facilitation outside the RF border from which slits could elicit facilitation was highly variable, ranging from less than 60 μm to about 300 μm, with the most typical facilitatory range lying between 60 and 120 μm.

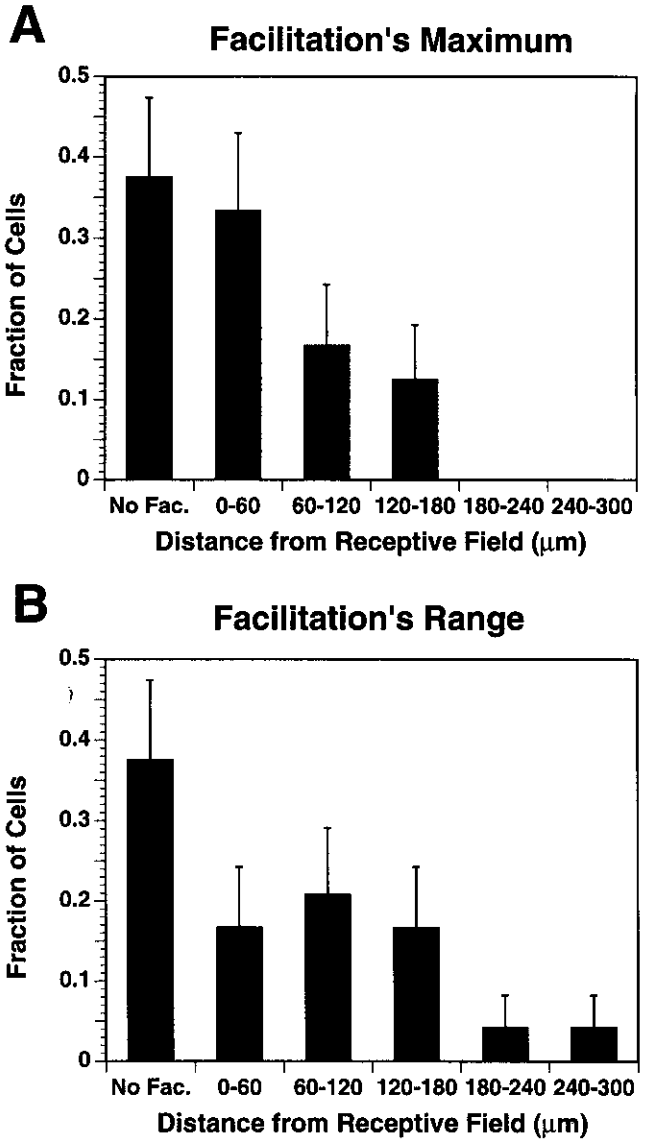

Fig. 4. The population statistics for the spatial parameters of preferred-direction facilitation, obtained with the protocols of Figs. 1C and 1D. A: The percentage of cells having maximal facilitation at particular distances from the excitatory RF center border. B: The percent of cells in which facilitation could be elicited at various distances. The error bars are the standard error bars for each bin assuming that the distributions follow a multinomial distribution, with each bin representing a separate category. In nine of 24 cells, we observed no statistically significant facilitation at any distance outside the RF center (see Discussion). In the other 15 cells, the spatial range of facilitation outside the RF border from which slits could elicit facilitation was highly variable, ranging from less than 60 μm to about 300 μm, with the most typical facilitatory range lying between 60 and 120 μm. The relatively narrow range of facilitation compared to inhibition is consistent with the previous findings of Grzywacz and Amthor in apparent-motion protocols inside the RF center (1993).

The spatial parameters of facilitation were similar for apparent motions ending just inside or just outside the RF (proto-

cols of Figs. 1C and 1D, respectively). However, facilitation was much harder to detect for spots placed just outside the excitatory RF center border, probably because the spot responses there still tended to be below threshold. Overall, there were no significant trends in the spatial parameters of facilitation as a function of the polarity (On or Off) of the stimulus contrast. That is, in some cells, facilitation was stronger for Off than for On stimuli, in others, the reverse was true. We did not explicitly test interactions between slit onset and spot offset (and *vice versa*) in these experiments because previous results using similar protocols within the excitatory RF center showed little significant cross-sign (On and Off) effects (Grzywacz & Amthor, 1993).

Discussion

Our experimental results show that both facilitation and inhibition of responses to spots within the excitatory RF center can be elicited from distances of 200 μm or more outside the excitatory RF center. These response modulations are asymmetric as a function of direction of motion, with facilitation occurring only for preferred-direction motions and inhibition occurring mostly for null-direction motions. This asymmetry, and the finding that facilitation occasionally requires a minimal distance before being optimal, suggest that facilitation depends on motion and is not simply summation of excitation, such as might be expected to occur within the RF center (see Grzywacz & Amthor, 1993 for a broader discussion on this issue). The data here confirm the existence of extra-receptive-field facilitation that was observed previously by Grzywacz and Amthor (1993, Fig. 6); in that study it was also shown that the directional tuning of facilitation is broad (>90 deg).

The failure to observe extra-receptive-field facilitation in 37% of the cells (Fig. 4) does not necessarily mean that some cells lack a facilitatory mechanism. Rather, the inability to detect facilitation may be due to variation in the balance between facilitation and surround inhibition (which clearly can be seen at large distances even in experiments where facilitation is significant at shorter ones, see Fig. 3). This inhibition might often be counteracted by preferred-direction facilitation due to short, but not long-distance motions, since the spatial range of facilitation is relatively narrow. Detection of facilitation may also be sensitive to the positioning of the facilitated spot in a region where the facilitation effect is suprathreshold. It is also possible that continuous motion in the preferred direction from the surround to the excitatory RF center border might provide a more effective facilitatory stimulus than the particular apparent motion protocol used here.

Because the majority of cells showed preferred-direction facilitation from outside the excitatory RF center, the data reported here suggest reassessing the objection raised by Yang and Masland (1992) to models of directional selectivity based on asymmetric excitatory-amacrine inputs to DS cells. There is considerable anatomical and pharmacological evidence (Masland & Ames, 1976; Ariel & Daw, 1982; Famiglietti, 1992) for the involvement, in retinal directional selectivity, of starburst amacrine cells whose processes extend considerably outside the DS ganglion cell excitatory RF center. Two such models, proposed by Vaney (1990) and Borg-Graham and Grzywacz (1992), postulated that starburst amacrine dendrites pointing (from cell body to dendritic ending, or tip) towards the preferred direction of a DS ganglion cell might contact that cell more often than dendrites pointing in the opposite direction. Because the release of acetylcholine is from the region near the dendritic tip of the amacrine cells, starburst dendrites just contacting the edge of the DS ganglion cell's dendritic tree (from where preferred-direction motions first enter the cell's excitatory RF center) would be expected to convey inputs to the DS ganglion cell from outside its own dendritic arborization. The coincidence between the spatial range of extra-receptive-field facilitation (Fig. 4) and the sizes of starburst amacrine cells at the same eccentricity (Tauchi & Masland, 1984) lends further support for these asymmetric amacrine models.

Yang and Masland argued that because the DS ganglion cell dendritic tree and excitatory RF center were relatively in good register, models such as those of Vaney, and Borg-Graham and Grzywacz involving the lateral spread of excitation from outside this area were untenable. Our data suggest, however, a different interpretation of Yang and Masland's results. The role of excitatory amacrine cells might be to modulate, *via* a motion-specific facilitation, the responses of DS cells to give rise to their directional selectivity. In this case, although the profile of the traditional RF might be dominated by direct bipolar inputs to the DS cell within the region of its dendritic arborization, facilitatory inputs, which themselves might not be capable of directly eliciting suprathreshold excitatory responses, could affect the ganglion cell from outside this region.

That significant, direction-of-motion specific facilitation is conducted from well outside the classical excitatory receptive-field center (and, therefore, dendritic arborization) of On–Off DS ganglion cells highlights the fundamental distinction between excitatory and facilitatory mechanisms in retinal ganglion cell receptive-field organization. One long-standing, well-studied precedent for this distinction is the McIlwain (shift) effect (1964), which is an example of a motion-sensitive, extra-receptive-field facilitation capable of elevating the maintained, or excitatory RF center modulation spiking activity of Y, and to a lesser extent, X and some W ganglion cells in cat. Although almost certainly mediated by a different mechanism than reported here, it serves as a classical forerunner for retinal processes whose action is primarily facilitatory, rather than directly excitatory themselves. Unraveling the biophysical basis of this example of a facilitatory mechanism in On–Off DS ganglion cells of the rabbit retina, and determining whether it is indeed based on cholinergic amacrine cells, is clearly an important challenge for future research efforts.

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