

Effects of Brain Stem Parabrachial Activation on Receptive Field Properties of Cells in the Cat's Lateral Geniculate Nucleus

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SUMMARY AND CONCLUSIONS

1. The lateral geniculate nucleus is the primary thalamic relay for the transfer of retinal signals to the visual cortex. Geniculate cells are heavily innervated from nonretinal sources, and these modify retinogeniculate transmission. A major ascending projection to the lateral geniculate nucleus arises from cholinergic cells in the parabrachial region of the brain stem. This is an important pathway in the ascending control of arousal. In an *in vivo* preparation, we used extracellular recordings to study the effects of electrical activation of the parabrachial region on the spontaneous activity and visual responses of X and Y cells in the lateral geniculate nucleus of the cat.

2. We studied the effects of two patterns of parabrachial activation on the spontaneous activity of geniculate cells. *Burst stimulation* consisted of a short pulse at high frequency (16 ms at 250 Hz). *Train stimulation* was of longer duration at lower frequency (e.g., 1 s at 50 Hz). The firing rate of almost all geniculate cells was enhanced by either pattern of stimulation. However, the burst pattern of stimulation elicited a short, modulated response with excitatory and inhibitory epochs. We found that the different epochs could differentially modulate the visual responses to drifting gratings. Thus the temporal alignment of the brain stem and visual stimuli was critical with burst stimulation, and varied alignments could dramatically confound the results. In comparison, the train pattern of stimulation consistently produced a relatively flat plateau of increased firing, after a short initial period of more variable effects. We used the less confounding pattern of train stimuli to study the effects of parabrachial activation on visual responses.

3. Our main emphasis was to examine the parabrachial effects on the visual responses of geniculate cells. For most visual stimuli, we used drifting sine wave gratings that varied in spatial frequency; these evoked modulated responses from the geniculate cells. Parabrachial activation enhanced the visual responses of almost all geniculate cells, and this enhancement included both increased depth of modulation and greater response rates.

4. Our results were incorporated quantitatively into a difference-of-Gaussians model of visual receptive fields in order to study the parabrachial effects on the spatial structure of the receptive field. This model fit our data well and provided measures of the response amplitude and radius of the receptive field center (K_c and R_c , respectively) and the response amplitude and radius of the receptive field surround (K_s and R_s , respectively). Parabrachial activation produced a fairly consistent elevation of K_c , and R_c was little affected, leading to an increase in the strength of the receptive field center (proportional to $K_c \cdot R_c^2$). The effects on K_s and R_s were more variable. Despite this variability, increases in K_s more than offset decreases in R_s (and vice versa), such that parabrachial activation also consistently increased the strength of the receptive field surround (proportional to $K_s \cdot R_s^2$). In some cells, surround and center strength increased proportionally, resulting in a proportionate increase at all spatial frequencies. In other cases, surround strength increased more than center strength, causing the cells to

behave more like high-pass filters. The reverse was found for other cells.

5. By most measures, geniculate X and Y cells were similarly affected by parabrachial activation. One notable exception is that K_c in X cells was increased significantly more than in Y cells. We suggest that this may relate to a morphological difference in retinogeniculate circuitry between cell types. Most retinal inputs to X cells are strongly affected by interneuron terminals, with which they form triadic contacts; retinal inputs to Y cells tend to be simpler and nontriadic. There is considerable parabrachial input to triads, affording the parabrachial region with a potentially powerful means of gating retinogeniculate transmission for X cells.

6. We confirm that parabrachial activation enhances the transmission of ascending visual information through the lateral geniculate nucleus. For almost all cells, the increase was observed at all spatial frequencies. The enhanced transmission of higher-frequency stimuli will better convey information about the details of a visual scene. In addition, the increase in the strength of the receptive field surround will maintain the lateral inhibitory mechanisms that are crucial for the enhancement of visual contrast edges. These combined effects will result in the transmission of a sharper visual image. This is what one would expect under conditions of increased alertness, and it is consistent with the idea that the parabrachial region is involved in arousal.

INTRODUCTION

The lateral geniculate nucleus in mammals is the primary relay of retinal input to cortex (Lennie 1980; Sherman 1985), and it is now clear that geniculate circuitry serves to gate or filter this relay selectively (McCormick 1992; Sherman and Koch 1986; Singer 1977; Steriade and Llinas 1988). This modulation in the thalamus, which may be an important neural correlate of varying attention or arousal and which also may accompany certain oculomotor events, is enabled through a variety of mechanisms controlled by extraretinal inputs (McCormick 1992; Sherman and Koch 1986; Singer 1977; Steriade and Llinas 1988), which in total make up 80–90% of the synaptic inputs onto geniculate relay cells (Wilson et al. 1984). These inputs include circuits intrinsic to the thalamus that largely involve local, inhibitory cells that use γ -aminobutyric acid (GABA) as a neurotransmitter; pathways descending from the visual cortex; and pathways from subcortical sources in the hypothalamus and brain stem.

The largest subcortical projection, in terms of axon density in the lateral geniculate nucleus and number of cells of origin, is the projection from the parabrachial region of the brain stem (DeLima and Singer 1987; Fitzpatrick et al. 1989).

The parabrachial region has been implicated in a variety of functions, including general arousal (Singer 1977; Steriade and Llinas 1988). Almost all (>90%) of the parabrachial cells that project to the lateral geniculate nucleus are cholinergic (DeLima and Singer 1987; Smith et al. 1988), and activation of this area or direct application of acetylcholine (ACh), either in vivo or in vitro, enhances the firing rate of geniculate cells and thereby the transmission of visual information through the lateral geniculate nucleus to the cortex (Francesconi et al. 1988; McCormick and Prince 1987; Sillito et al. 1983). This enhancement from the parabrachial region is achieved through at least three different means: 1) the cholinergic axons from the parabrachial region directly depolarize relay cells (Hu et al. 1989; McCormick and Prince 1987); 2) these same cholinergic axons hyperpolarize the local GABAergic cells, thereby disinhibiting relay cells (Ahlsen et al. 1984; Singer 1977); and 3) parabrachial activation and/or ACh application will affect voltage-dependent conductances (McCormick 1992; Steriade and Llinas 1988). As an example of the last point, parabrachial activation and/or ACh application prevents relay cells from bursting and promotes their more tonic, faithful relay of retinal inputs to cortex (Lu et al. 1993; McCormick 1992).

Although several studies have described effects of parabrachial activation on responsiveness of relay cells, little attention has been focused on the effects of such stimulation on receptive field structure. Receptive fields of retinal and geniculate X and Y cells have an antagonistic, concentric center-surround organization. Although the center response of a geniculate cell is thought to derive primarily from the retina, the surround response appears to be enhanced in the lateral geniculate nucleus via inhibitory inputs from local GABAergic cells (Dubin and Cleland 1977; Eysel et al. 1986). One approach for studying receptive field organization is provided by linear systems analysis (Shapley and Lennie 1985), whereby one measures the responses of cells to sinusoidal gratings that can be varied across a range of spatial and temporal frequencies. With Fourier techniques, one can then predict a cell's linear response to a variety of stimuli. Using Fourier techniques it is also possible to model receptive field organization of geniculate cells by the difference of two overlapping Gaussian functions, one for the center and one for the surround; each function has a height that reflects sensitivity or amplitude of response and a width that reflects radius (Linsenmeier et al. 1982; Shapley and Lennie 1985; So and Shapley 1981). That is, it is possible to assess separately the center and surround of a geniculate cell by analyzing its responses to a range of spatial frequencies. More complex models have been proposed that deal with offsets in alignment or phase differences of the center and surround and various nonlinearities (e.g., Dawis et al. 1984; Enroth-Cugell and Freeman 1987; Hockstein and Shapley 1976a,b; Kaplan 1991; Kaplan et al. 1979; Soodak et al. 1987). However, the difference-of-Gaussians model provides a reasonable first approximation. This approach, which is the purpose of the present study, has not been used previously to study the effects of parabrachial activation on the visual responses of geniculate cells.

METHODS

We performed these experiments on normal adult cats during acute electrophysiological recording sessions. Throughout, we used

standard procedures that are briefly outlined here. The cats were deeply anesthetized (4% halothane in a 1:1 mixture of N₂O and O₂), cannulated, intubated, and placed in a stereotaxic apparatus where they were paralyzed (5 mg gallamine triethiodide), artificially respired, and surgically prepared for craniotomies to enable intracranial entry of recording and stimulating electrodes. We continuously monitored heart rate and cortical electroencephalogram (EEG). End-tidal CO₂ was maintained at $4 \pm 0.2\%$ and body temperature at $38 \pm 0.5^\circ\text{C}$. Wound margins and pressure points were infused with 2% lidocaine. During all succeeding surgical procedures, we kept halothane levels between 1 and 2%. During recording, the halothane was reduced to 0.4–0.8% and paralysis was maintained with an intravenous infusion of gallamine triethiodide ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and *d*-tubocurarine ($0.35 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$).

To dilate the pupils and retract the nictitating membranes, we topically applied atropine sulfate and phenylephrine hydrochloride. We did not administer atropine systemically because of its effects on the cortical EEG (Hammond 1978) and because it interferes with cholinergic functioning and the effects of parabrachial activation (Eysel et al. 1986). The corneas were covered with contact lenses chosen by slit retinoscopy to focus the retinas on a cathode ray tube 57 cm in front of the eyes. In some of the later experiments, artificial pupils 3 mm diam were used. We found very little improvement in resolution using the artificial pupils.

At the end of the experiment the animal was given a bolus of pentobarbital sodium and perfused with aldehyde fixatives. The lateral geniculate nucleus and brain stem were then sectioned to verify recording and stimulation sites. In all cases reported here, cell recording locations were verified within the geniculate A laminae, and stimulating electrodes were well placed in the parabrachial region.

Electrical stimulation

We placed a pair of bipolar stimulating electrodes across the optic chiasm at A14, L1.0–L1.5; we determined depth by maximizing a visually evoked potential. Another pair of stimulating electrodes was placed in the parabrachial region ipsilateral to the lateral geniculate nucleus in which we were recording. We used various strategies in early experiments to place stimulating electrodes in the parabrachial region (described in Uhlrich et al. 1988). However, in later experiments we found that simple stereotaxic placement of the electrodes worked well, targeting the rostral portion of the parabrachial region at AP0, L1 and L3–4, and H-1 (9 mm above the ear bar). Effective placement was confirmed before cementing the electrodes in place by observing that the potential evoked in the lateral geniculate nucleus by optic chiasm stimulation was increased by parabrachial activation. In all cases, electrode placements were histologically confirmed. Figure 1 shows the location of the stimulating electrodes in the parabrachial region for a typical experiment.

We activated the parabrachial region with positive current pulses 50–100 μs in duration and 150–700 μA in amplitude. These were delivered in short bursts or trains: *burst stimulation* consisted of 3–5 pulses at 250 Hz, whereas *train stimulation* was performed at 25–50 Hz for 500–1,000 ms. Both burst and train stimulation produced a pronounced enhancement in the visual responses of most geniculate cells. However, as noted more fully in RESULTS, most of the data reported here were collected using train stimulation, chiefly because burst stimulation produced a relatively short, uneven effect with various peaks and troughs. These undulations confounded our analysis of the modulated visual response (see below). In contrast, after a brief transient seen in some geniculate cells, the effects on responsiveness of train stimulation were quite flat. Changes in the depth of modulation of the response could thus be more readily interpreted as a change in the visual response rather than ascribed to a poststimulation brain stem effect per se.

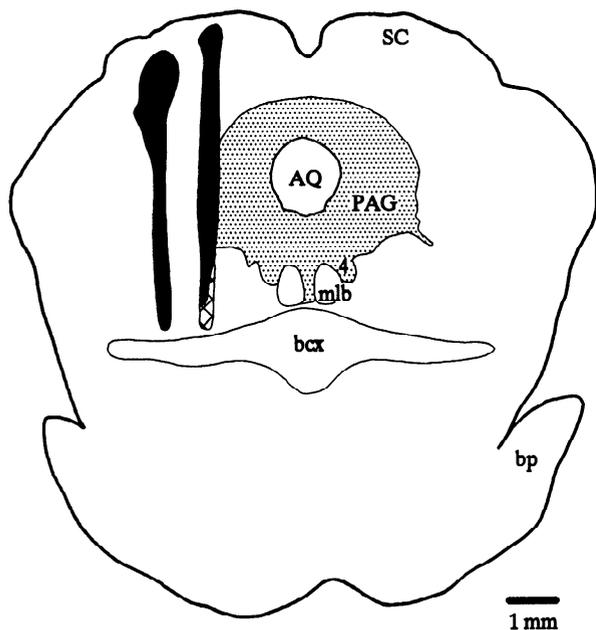


FIG. 1. Cameral lucida reconstruction of a representative stimulation site in the rostral parabrachial region. Solid shading: electrode tracks. Hatched shading at bottom of the medial track: location of the track at its full depth in an adjacent section. AQ, cerebral aqueduct; PAG, periaqueductal gray; SC, superior colliculus; bcx, decussation of the brachium conjunctivum; bp, brachium pontis; mlb, medial longitudinal bundle; 4, trochlear nucleus.

Electrophysiological recording

We used glass pipettes filled with 3 M KCl and beveled to a final impedance (at 100 Hz) of 10–20 M Ω to record cells from the lateral geniculate nucleus. In some penetrations the pipettes were filled with tris(hydroxymethyl)aminomethane-buffered 0.2 M KCl and beveled to an impedance of roughly 60 M Ω (cf. Humphrey and Weller 1988). We sometimes included Pontamine sky blue in the electrodes so that recording sites could be identified in subsequent histology.

Cell classification

Once we isolated a cell, we plotted its receptive field on a tangent screen and then physiologically characterized it as a W, X, or Y cell using a battery of tests (Sherman 1985). These included latency to optic chiasm stimulation, linearity of summation to a counterphase-modulated grating stimulus, receptive field center size, response to large, fast-moving discs, phasic or tonic response to standing contrast, and receptive field sign (ON and OFF center). We then identified a subset of the recorded cells as displaying lagged or nonlagged onset responses chiefly on the basis of onset and offset response latencies to a flashed, centered spot (Humphrey and Weller 1988; Mastrorarde 1987).

Visual stimulation

Visual stimuli consisted of vertical sinusoidal gratings or spots of light generated on the screen of a cathode ray tube that was driven by a computer-controlled function generator. Space-averaged luminance was 40 cd/m², and contrast of the gratings, defined as $(L_{\max} - L_{\min}) / (L_{\max} + L_{\min})$, where L_{\max} is maximum luminance and L_{\min} is minimum luminance, could be continuously varied between 0 and 60%. Gratings were counterphase modulated to determine response linearity and were drifted horizontally at 4 Hz to obtain spatial tuning curves based on responses to five to nine

different spatial frequencies. A typical single trial consisted of three parts, all of which included visual stimulation in which a grating of selected spatial and temporal frequencies drifted across the receptive field of the cell: 1) a 1-s (sometimes 0.5-s) control period of visual stimulation only; 2) a 1-s (sometimes 0.5-s) period during which the brain stem was also stimulated; and 3) a 1-s (sometimes 0.5-s) period after termination of the brain stem stimulation to observe recovery of the response. In addition to the drifting gratings, we also obtained measures of spontaneous activity and responses to full-field illumination. For spontaneous activity we presented trials in which the contrast of the oscilloscope screen was 0 but with the same space-averaged luminance as used for the gratings. For full-field illumination, the homogeneous face of the cathode ray tube was sinusoidally modulated at 4 Hz through the same modulation depth as used for the drifting gratings. There was a brief 1.5- to 3-s pause between trials to allow the brain stem effect to dissipate. During the intertrial pause, spike data were written to disk and a new spatial frequency (or a trial for spontaneous activity or full-field illumination) was selected. Spatial frequency was chosen in a block random style; that is, frequencies were chosen randomly without replacement until all frequencies in the set were used. Then the procedure was repeated. The data presented here are from cells in which each data point was obtained from ≥ 10 trials. For most cells, >25 trials were obtained at each condition.

For quantification of visual responses, action potentials from recorded cells were fed through a window discriminator into the computer, where histograms synchronized to the temporal stimulus cycle were generated and stored for both on- and off-line analysis. Data from each visual stimulus condition were pooled and histograms generated from them. These were Fourier analyzed to obtain amplitude measures of the overall average firing rate (F0), the fundamental temporal frequency (F1), and the second harmonic (F2) of the cell's response to each spatial frequency. F1 values were then plotted as a function of spatial frequency to generate the cell's spatial tuning curve. The points on the tuning curves were then approximated by functions representing the difference of two Gaussian functions, which represent responses from the receptive field's center and surround (Linsenmeier et al. 1982; Rodieck 1965; Shapley and Lennie 1985). The amplitude and diameter of both the center and surround were then estimated by this analysis.

RESULTS

We recorded extracellularly from 187 geniculate cells in 18 cats. Of these, 96 were identified as X cells, 98 as Y cells, 2 as W cells, and 1 as unclassified, having properties that seemed mixed between those of X and Y cells (Sherman 1985). In addition, we recorded from 6 geniculocortical Y axons in the radiations just above the lateral geniculate nucleus (these were regarded as geniculate Y cells) and 12 retinal axons (6 X cells, 6 Y cells) in the optic tract just below the lateral geniculate nucleus. We tested 51 geniculate X cells and 16 Y cells with flashing spot stimuli. Four of the X cells exhibited a lagged response to stimulus onset and offset; five exhibited a lagged response only to stimulus onset. No lagged Y cells were encountered. Cells were sampled throughout the lateral geniculate nucleus; receptive field eccentricities ranged from the area centralis to 51°, and of the 193 geniculate receptive fields, 176 (91%) were found within the central 20°. Our main goal here was to assess the effects of parabrachial activation on receptive field properties of these cells. In the account below, not every cell was tested for every analysis, but the relevant numbers are given where appropriate.

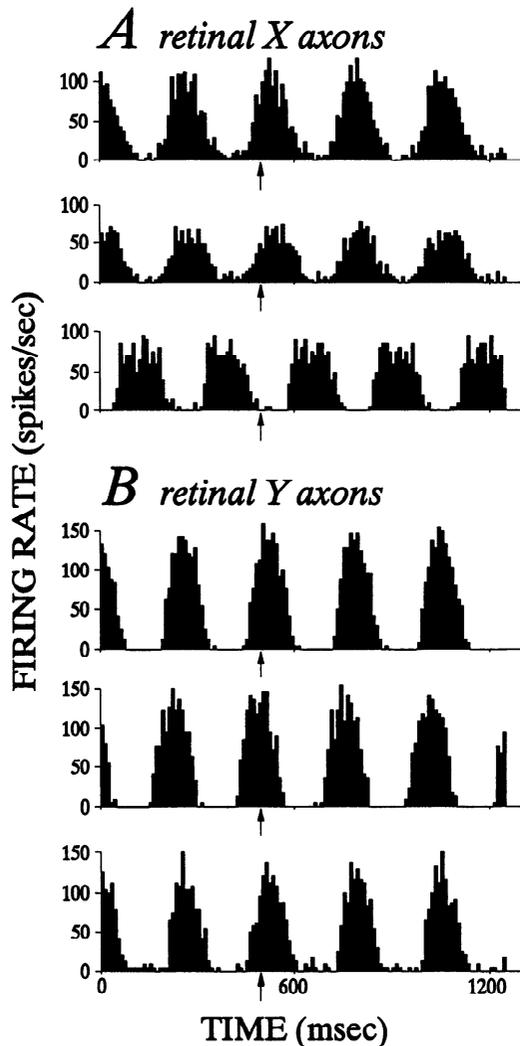


FIG. 2. Responses of retinal ganglion cell axons to drifting sinusoidal gratings with and without parabrachial activation. Arrow below each histogram: onset of parabrachial burst activation. Note that parabrachial activation has no discernible effect on these responses. *A*: responses of 3 X axons. *B*: responses of 3 Y axons.

Lack of effects of parabrachial activation on retinal axons

We have briefly examined the effects of brain stem stimulation on the spontaneous and visual responses of the 12 retinal axons (6 X cells, 6 Y cells) noted above. Figure 2 shows representative examples from three X and three Y axons. No effects of parabrachial activation were detected. This implies that the changes induced in geniculate cells by parabrachial activation that we describe below are not a simple reflection of changes in the retinal afferent but instead reflect a change in retinogeniculate transmission.

Effects of parabrachial activation on spontaneous activity

Parabrachial activation induced an increase in the spontaneous activity of 44 of 49 X cells (90%), 42 of 51 Y cells (82%), both W cells, and the mixed XY cell. The remaining five X and nine Y cells were inhibited by parabrachial activation. For both the X and Y cell populations, these increases are statistically significant ($P < 0.001$ on a binomial test for each cell type). The time course of the effect depended

on the parameters of parabrachial activation that we used. As described in METHODS, we employed two different stimulation paradigms, the burst and train paradigms. Although both paradigms produced an increase in the firing rate of most geniculate cells, there were marked differences in the time course of effect. Short bursts of stimulation produced relatively short, modulated effects (e.g., Figs. 4C and 3A). In contrast, trains of parabrachial activation sometimes elicited an initial transient response, but thereafter produced a relatively flat increase in firing rate (e.g., Fig. 8).

Effects of parabrachial activation on responses to visual stimulation

GENERAL RESPONSIVENESS. Certain effects of parabrachial activation on the responses of geniculate cells to visual stim-

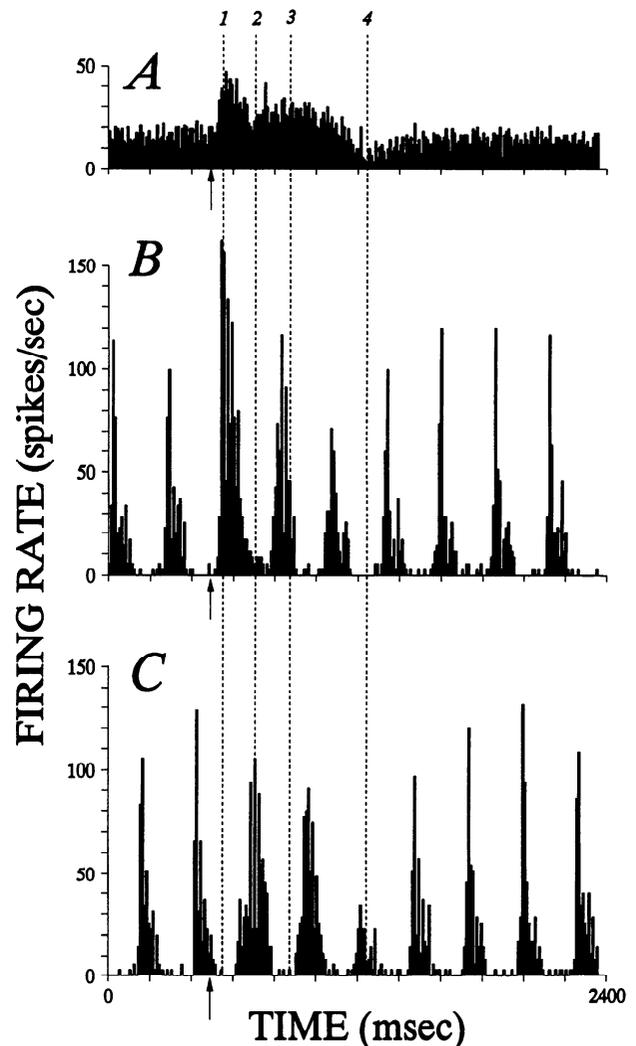


FIG. 3. Effects of parabrachial burst activation on a geniculate Y cell. Arrow below each histogram: onset of parabrachial activation. *A*: effect on spontaneous activity. Four epochs of the response, labeled 1-4, are identified, and the alignment of these epochs among the 3 histograms is indicated by the 4 vertical dashed lines. *B*: effect of the same parabrachial activation on the response of the cell to a drifting grating. The relative phase of parabrachial and visual activation was arranged such that the excitatory peak of the visual response aligned with parabrachial epochs 1 and 3. *C*: effect of the same parabrachial activation when the relative phase of the parabrachial and visual activation is adjusted such that the excitatory peak of the visual response aligned with parabrachial epochs 2 and 4.

ulation have been reported previously (e.g., Francesconi et al. 1988; Fukuda and Stone 1976; Hartveit and Heggelund 1992; Hartveit et al. 1993; Humphrey and Saul 1992; Singer 1977). Many of these studies employed burst activation. Figure 3 illustrates a complication that is associated with parabrachial burst activation. As shown in Fig. 3A, such burst activation produces a series of changes in the spontaneous firing rate of the cell. There are four such epochs, labeled 1–4 and identified in all histograms by the numbered, dashed lines: epoch 1 represents a firing increase of short latency and duration; epoch 2 represents a short-latency decrease from the earlier peak of firing; epoch 3 represents a longer-latency and longer-duration increase in firing; and epoch 4 represents a second, brief suppression of firing. Figure 3, B and C, shows the same parabrachial activation paired with a visual stimulus that is modulated sinusoidally in time. In Fig. 3B, the visual stimulus is aligned temporally to superimpose the first two peaks of visually evoked response with epochs 1 and 3 (i.e., parabrachial-induced increases in spontaneous activity), and the visually evoked troughs are aligned with epochs 2 and 4 (i.e., parabrachial-induced decreases in spontaneous activity); in Fig. 3C, the alignment is reversed, so that epochs 1 and 3 coincide with visually evoked troughs and epochs 2 and 4 with visually evoked peaks. Clearly, the four epochs seen in response to parabrachial activation differentially affect the visual response of the cell. Therefore the temporal alignment of the brain stem and visual stimuli is critical when one uses the burst stimulation paradigm, and it is difficult to control for these alignment effects. Indeed, most previous studies using burst stimulation have failed to provide such control when attempting to discern the effects of parabrachial activation on the visual responses of geniculate cells.

Another problem that is inherent in the results of many prior studies is illustrated in Fig. 4. Figure 4A shows the response of a Y cell to a full-field visual stimulus flashed on and off as indicated. This cell produced transient responses at stimulus onset and offset. Figure 4B shows the response of the cell to the same visual stimulus when stimulus onset was preceded by 100 ms with parabrachial burst activation. The cell responded with what could be described as an increase in the sustained component of its response. However, Fig. 4C, which has been shifted to the left to line up the beginning of parabrachial activation with that in Fig. 4B, shows the effect of the same parabrachial burst activation on spontaneous activity. Such burst activation alone produced an elevated response in the Y cell that could account for most of the effect seen in the *middle trace*. Thus, in the *middle trace*, it is difficult to distinguish the specific enhancement of visual driving from the simple effects of parabrachial activation per se. Such uncertainty results when the effects of parabrachial activation are aligned temporally only with the visual response.

Thus we have modified our paradigm in three important ways to minimize the problems illustrated by Figs. 3 and 4. First, we used parabrachial train activation, which, after a variable early transient, does not produce a modulated effect and acts for a longer duration. This makes the parabrachial activation less critically dependent on its temporal relationship with the visual stimulus. Second, instead of a flashing spot or similar pulsed stimulus, we used a periodic visual stimulus, which was a drifting sinusoidal grating. This was

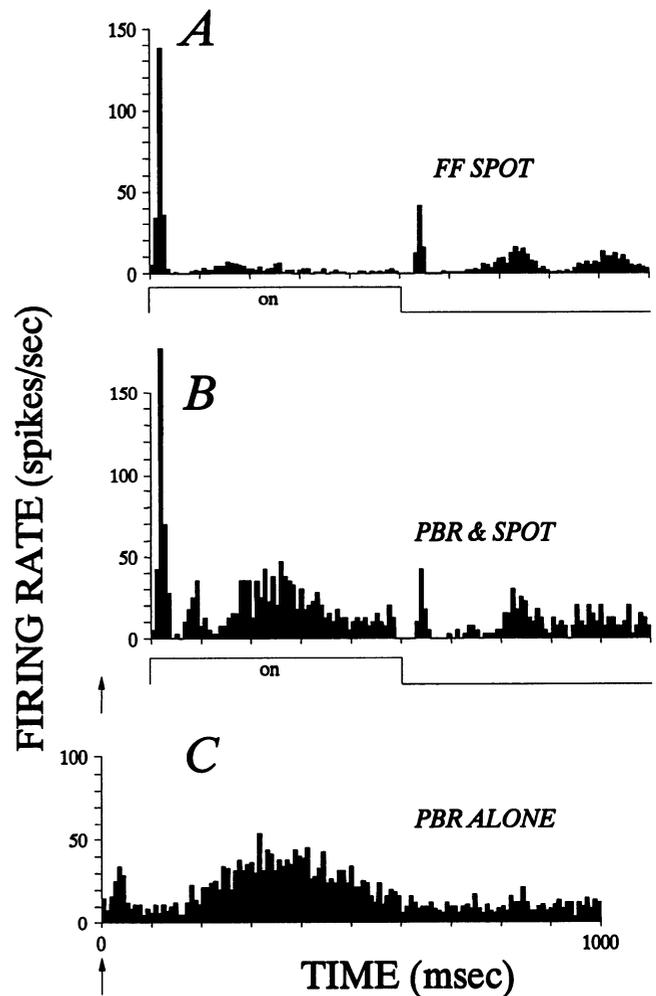


FIG. 4. Effects of parabrachial burst activation on a geniculate Y cell. A: response to a full-field (FF) stimulus, flashed on and off as indicated below the histogram. B: response to the same visual stimulus when parabrachial burst activation preceded spot onset by 100 ms. C: effect of parabrachial burst activation on spontaneous activity. Arrows in B and C: onset of parabrachial activation. Note that the histogram shown in C is shifted to the left so that onsets of parabrachial activation are aligned temporally.

designed to change the depth of modulation in the firing pattern with minimal effects on the overall firing rate. Because parabrachial train activation that is asynchronous with the drifting grating would not be expected to change this depth modulation through any direct effect on the geniculate neuron, any change seen with such parabrachial activation implies an effect on responses to visual stimuli. It should also be noted, as described in INTRODUCTION, that such sinusoidal visual stimulation offers the advantage of a powerful quantitative model of receptive field organization (Shapley and Lennie 1985). Third, we increased the duration of the train stimulation so that it spanned several of the visual stimulus cycles. This further reduces the likelihood that this stimulation affects any limited region of the stimulus-response cycle and instead ensures that the effects of parabrachial activation can be discerned throughout the cycle.

Representative examples of the responses of geniculate cells to drifting sine wave gratings and the effects of parabrachial activation are shown in Fig. 5. The typical response of the geniculate cells to the drifting grating is a modulated

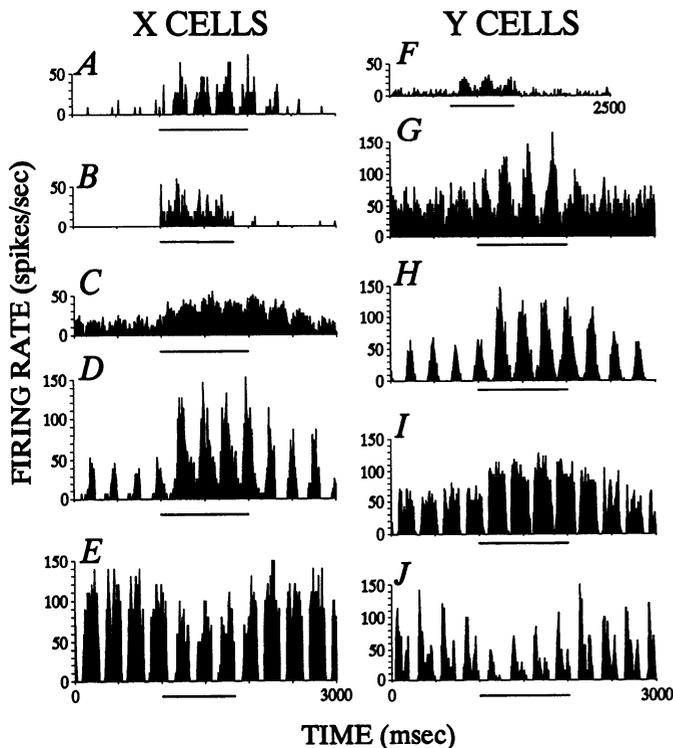


FIG. 5. Representative effects of parabrachial train activation on the responses of geniculate cells to drifting sinusoidal gratings. Solid line below each histogram: duration of parabrachial activation. *A-E*: responses of 5 X cells. *F-J*: responses of 5 Y cells.

response as the brighter and darker cycles of the grating rhythmically drift across the receptive field of the cell. At the grating contrast used in these experiments (generally 40%), the depth of modulation usually exceeds background firing, resulting in a nonlinear bottoming out or partial rectification of the response. Nonetheless, for nearly all geniculate cells, parabrachial activation clearly enhances responses to visual stimulation (see below for further details). Figure 5, *A-D* and *F-I*, shows examples of such enhancement. This enhancement takes several forms. In most cases the depth of modulation appeared to increase, and examples are shown in Fig. 5, *A*, *D*, and *F-I* (see also below). Because the response was rectified in most cases, the average number of spikes increased as well. In other cases the modulated component of the response did not change significantly, but the baseline level did, and an example of this is seen in Fig. 5*C*. In rare cases, parabrachial activation reduced visual responsiveness, and Fig. 5, *E* and *J*, shows one example each for an X and Y cell.

TIME COURSE OF RESPONSE. For some cells, parabrachial activation affected the shape or time course of the visual response. This has been most dramatically illustrated for X cells showing lagged responses, for which parabrachial activation dramatically reduces the latency of response to visual stimulation (Hartveit and Heggelund 1993; Humphrey and Saul 1992; Uhrich et al. 1990). Figure 6 shows further examples in which parabrachial activation caused changes in the time course of responses to drifting gratings. Here responses of two X and two Y cells are shown before, during, and after parabrachial activation. It is possible from such

data to obtain the Fourier components of the response, including the F1 component and its relative phase. In three of the examples (Fig. 6, *A-C*), parabrachial activation caused a relative phase advance of the response, which means the response occurred sooner after the visual stimulus. We added a control in these phase analyses to avoid artifacts caused by eye movements. That is, in some experiments parabrachial activation caused small convergent eye movements. A small eye movement in the direction of the moving grating would cause the response to appear later as an apparent phase lag, and an eye moving in the opposite direction of the grating would cause an apparent phase advance. For the cells shown in Fig. 6, we controlled for this by measuring the phase of the response to gratings moved in both directions. Because the measured phase effect was the same regardless of the direction of grating motion, we concluded that for these cells these analyses are not contaminated by eye movements.

A range of temporal frequencies from 3 to 6 Hz was used for the examples in Fig. 6. The relative phase advances and latency reductions were 2.5 rad and 131.5 ms for Fig. 6*A*, 2.5 rad and 103.7 ms for Fig. 6*B*, and 0.8 rad and 33 ms for Fig. 6*C*. The two X cell responses are from lagged X cells, and this advance was common for cells that exhibited lagged responses. The Y cell in Fig. 6*C* was not identified as to lagged or nonlagged type and was the only Y cell to exhibit a large phase advance with parabrachial activation. There was virtually no phase advance for the nonlagged Y cell of Fig. 6*D* (0.1 rad and 2.7 ms), although parabrachial activation nonetheless altered the shape of the visual response. It should be noted that, without further tests, it is generally not possible to formally distinguish the difference between a phase advance and latency reduction, but the main point is that parabrachial activation could cause the response to occur earlier to visual stimulation.

We found a different result for cells that responded to each stimulus cycle with a high-frequency burst of spikes followed by a more linear response. For such cells parabrachial activation caused the bulk of the response to occur later. As has been recently shown (Guido et al. 1992; Lu et al. 1992), the early barrage of spikes occurs when cells are in the burst mode of firing, and parabrachial activation switches cells from burst mode to relay (or tonic) mode, eliminating the early burst. Figure 7 shows an X and Y cell exhibiting such behavior. Note the transient peak leading each response cycle before parabrachial activation and the elimination of this peak during such activation (Fig. 7, *A* and *C*). For these responses, Fig. 7, *B* and *D*, shows the ongoing Fourier analyses, which we determined in the following manner. We Fourier analyzed the response in a temporal window one cycle in extent; we started this analysis at the beginning of the trial, repeated this by shifting the window four bins later, and continued to analyze each window four bins later until the trial ended. Although parabrachial activation increases the overall response (F0) and linear response (F1) components, it reduces the F2 component, which is a nonlinear distortion in the response. Thus, by converting the cell's firing mode from burst to relay and thereby removing the early burst, parabrachial activation causes these cells to sum more linearly in their responses to visual stimuli.

The responses illustrated above from lagged cells and those in which the firing mode changed from burst to relay

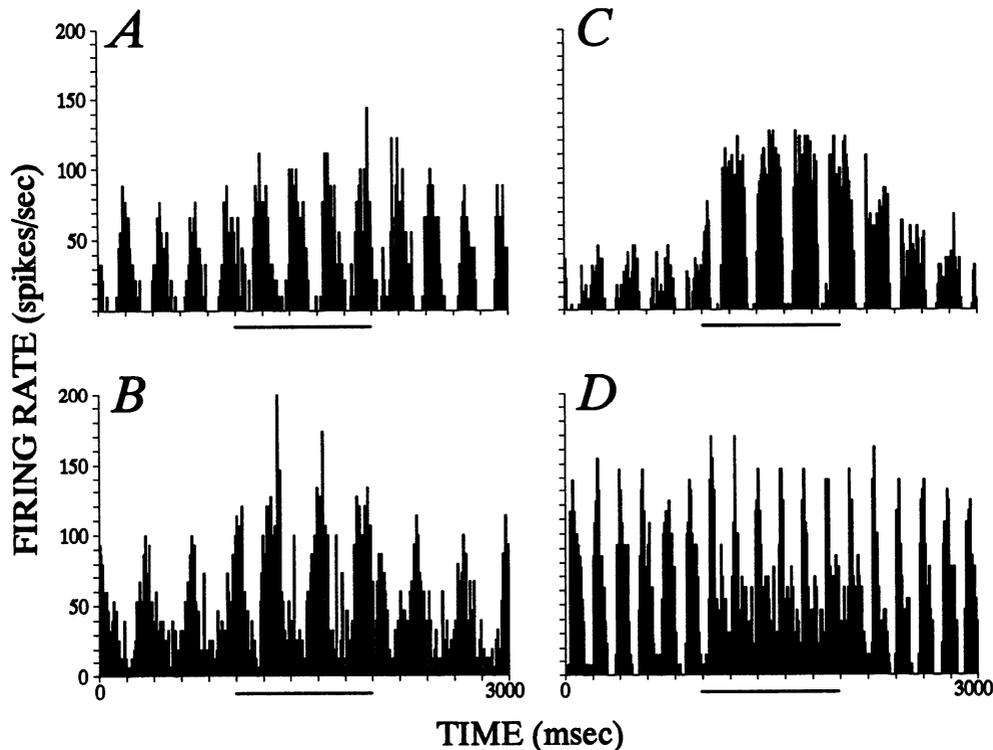


FIG. 6. Examples of geniculate cells for which parabrachial activation changed the time course of the visual response to drifting gratings. In each case the response occurred earlier during parabrachial activation. *A*: X cell showing a relative phase advance of 2.5 rad or a latency reduction of 131.5 ms. *B*: X cell showing a relative phase advance of 2.5 rad or a latency reduction of 130.7 ms. *C*: Y cell showing a relative phase advance of 0.8 rad or a latency reduction of 33 ms. *D*: Y cell showing a relative phase advance of 0.1 rad or a latency reduction of 2.7 ms.

represent the examples in which the timing of the visual response was altered by parabrachial activation. The majority of the cells in our sample did not exhibit a change in the phase or the time course of their visual response. The average phase change of nonlagged responses was 0.02 ± 0.16 rad, which for a 4-Hz drift frequency corresponds to a latency shift of 0.8 ± 6.2 ms. This also means that, with few exceptions, parabrachial activation did not differentially affect the phase of center versus surround.

EFFECTS OF PARABRACHIAL ACTIVATION ON FOURIER COMPONENTS. Although Fig. 7 shows a continuous record of the effects of parabrachial activation on the Fourier components of the visual response, we sought a means of comparing these parabrachial effects with equivalent control periods of visual stimulation without parabrachial activation. Figure 8 illustrates how we did this. Each trial contained 3 s of response to a grating drifted through the cell's receptive field at 4 Hz, and thus 12 cycles are included in each trial. The response from trial onset to onset of parabrachial activation was denoted the control (Fig. 8, *CONTROL EPOCH*) response. The timing of the parabrachial activation is shown at the *bottom of each histogram*. During the first 300 ms after the onset of parabrachial activation, we did not include the responses in our further analyses, because responses during this period were often unstable and exhibited transient effects. The remainder of the response during parabrachial activation (Fig. 8, *PBR EPOCH*) was included. We then computed a Fourier analysis of the averaged responses during the two periods, determining various Fourier components. We focused on the

overall response (F0) component, which represents the average number of spikes per stimulus cycle, and the F1 component, which had the same temporal frequency as that of the drifting gratings and reflects the linear, modulated response of the cell; we also could, if needed, compute other components, such as the F2 component, a nonlinear distortion product at twice the frequency of F1. Although the effects of parabrachial activation extend past the time at which the activation is terminated, we did not analyze this portion of the response because it proved too variable from cell to cell. However, note that the elevated response evoked by parabrachial activation during spontaneous activity returned rapidly back to baseline levels, whereas the parabrachial effects on the visual response declined much more slowly. The final third of each trial was not quantified; it was used primarily to monitor recovery back to control levels after parabrachial activation. We included a 1.5- to 3-s pause between trials, and this ensured a full recovery before the start of the next trial. Unless otherwise noted (e.g., during spatial tuning analyses), gratings were drifted at 4 Hz at a spatial frequency that evoked the maximum response.

EFFECTS ON SPONTANEOUS VERSUS VISUALLY DRIVEN ACTIVITY. Figure 9 compares the effects of parabrachial activation on spontaneous versus visually driven activity. Because there is no modulated response during spontaneous activity, we used only the F0 response measure for this comparison. As Fig. 9 shows, parabrachial activation resulted in an increase in both F0 components for nearly all cells, and most of the cells with the largest decrease in response showed

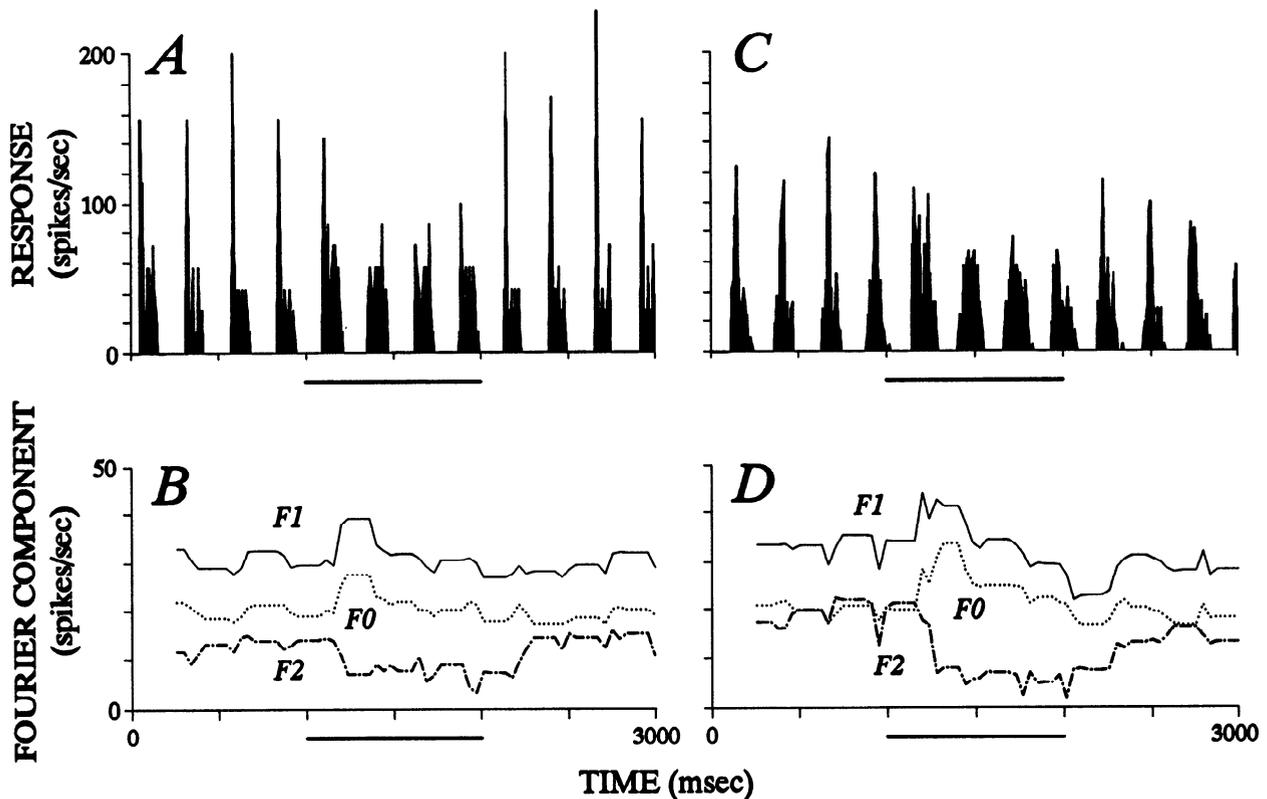


FIG. 7. Examples of geniculate cells for which the response to a drifting sinusoidal grating was changed from a burst mode to a more linear tonic mode by parabrachial activation. Solid bar in each panel: duration of parabrachial activation. *A* and *C*: actual responses of the cells. *B* and *D*: results of a Fourier analysis of the responses in which the average overall response (F0) plus the amplitudes of the fundamental (F1) and 2nd harmonic (F2) response components are indicated for each location along the histogram (see text for details). *A* and *B*: X cell response to an $0.5\text{-c}/^\circ$ grating. *B* and *D*: response of a Y cell to an $0.25\text{-c}/^\circ$ grating.

such reduction for both spontaneous and visually driven activity. We found no difference in the *relative* increase of the F0 component during spontaneous or visually driven responses ($P > 0.1$ on binomial tests for all comparisons). However, a comparison of the *absolute* number of increased spikes due to parabrachial activation shows a greater effect during visual stimulation ($P < 0.05$ for X cells; $P < 0.01$ for Y cells; binomial tests). Finally, for both X and Y cells, there is a significant correlation between the effects on spontaneous and visually driven activity ($r = +0.38$ and $P < 0.05$ for X cells; $r = +0.41$ and $P < 0.01$ for Y cells).

EFFECTS ON OVERALL AND MODULATED RESPONSES. Parabrachial train activation significantly enhanced both the F0 and F1 components of geniculate cells in response to visual stimulation. Figure 10 summarizes these effects as frequency histograms for the percent of change induced in the F0 and F1 components. Although parabrachial activation occasionally reduces these response components, for many more cells these components were increased: for the F0 response component, 36 of the 40 X cells and 45 of the 48 Y cells increased; and for the F1 component, increases occurred for 34 X cells and 37 Y cells ($P < 0.001$ on binomial tests for each analysis). Because with our methods we could not unambiguously distinguish between relay cells and interneurons, it is possible that some of the variability seen here is a result of including a small number of interneurons in our analyses. It is interesting in this regard to note that although ACh (a major transmitter

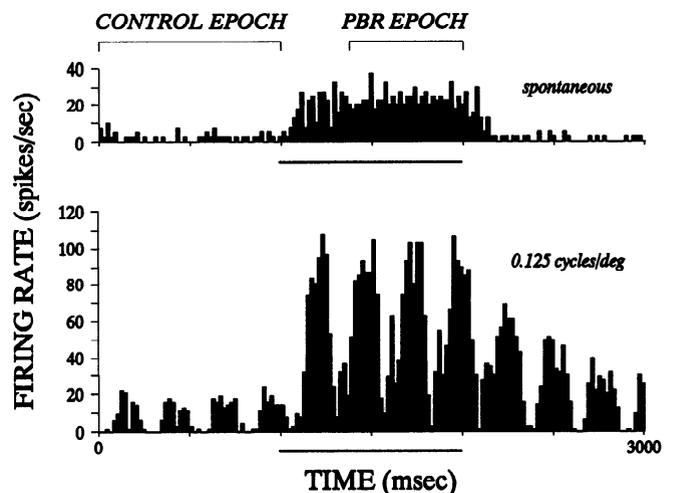


FIG. 8. Example of method used to quantify effects of parabrachial train activation (see text for details). Solid bar beneath each response histogram: duration of parabrachial activation. Control data were taken from trial onset until the onset of parabrachial activation (*CONTROL EPOCH*). Data for effects of parabrachial activation were taken during this activation, excluding the initial 300 ms, during which uneven or transient effects might occur (*PBR EPOCH*). *Top*: effect of parabrachial activation on spontaneous activity. *Bottom*: effect of parabrachial activation on response to drifting sinusoidal grating.

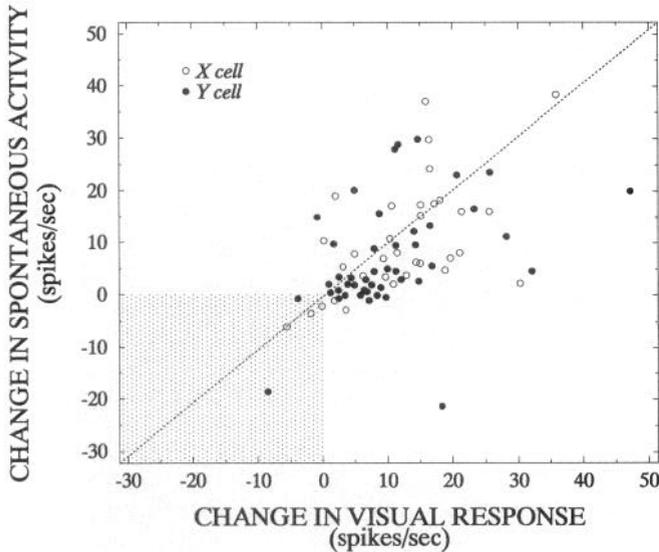


FIG. 9. Comparison of the effect of parabrachial train activation on the spontaneous and visually driven activity of geniculate X and Y cells. Each axis represents the change in the average number of spikes induced by parabrachial activation. For these visually driven responses, the optimal spatial frequency (i.e., that evoking the largest modulated response) was used. Dotted region: reduced activity resulting from parabrachial activation. Diagonal dashed line: slope = 1.

for parabrachial axons) excites relay cells, it inhibits interneurons (McCormick and Pape 1988; McCormick and Prince 1987). It is thus plausible to suggest that at least some of the cells showing reduced responsiveness during parabrachial activation may be interneurons.

For a subset of 27 of the 40 X cells shown in Fig. 10, we also employed tests to determine their lagged or nonlagged responses (see METHODS). Of these, two displayed lagged responses to stimulus onset and offset. Three others were "partially lagged" and displayed lagged responses only to stimulus onset. Despite the small sample size, we noticed statistically significant differences in the effects of parabrachial activation on these different responses. For the F0 component, lagged and partially lagged responses were enhanced 84% versus an increase of only 49% for the nonlagged responses ($P < 0.05$, Mann-Whitney U test). An even greater difference was found for the F1 component, which increased only 25% for the nonlagged responses but more than doubled (103%) for lagged responses ($P < 0.01$, Mann-Whitney U test).

The induced changes in the two Fourier components shown in Fig. 10 were significantly correlated for both cell groups ($r = +0.81$ for the X cells and $r = +0.95$ for the Y cells; $P < 0.001$ for each correlation). Interestingly, parabrachial activation generally led to greater increases in the F0 component than in the F1 component for both X and Y cells. This was true for 34 of the 40 X cells and 43 of the 48 Y cells ($P < 0.001$ on binomial tests for each cell class). Parabrachial activation thus appears to elevate baseline firing more than it increases the depth of modulation for these geniculate cells.

EFFECTS OF PARABRACHIAL ACTIVATION ON SPATIAL TUNING. We found that for most cells the effect of parabrachial activation depended on the spatial frequency of the visual stimulus.

We systematically examined this by recording trials like that depicted in Fig. 8 but varying the spatial frequency of the grating in a randomly interleaved fashion. In this manner we obtained spatial frequency tuning curves before and during parabrachial activation from 39 X and 44 Y cells. We found no significant differences between lagged and nonlagged X cells in any of the analyses described below. Thus data from these X cell types are pooled. Representative examples for X cells are shown in Fig. 11, and examples for Y cells are shown in Fig. 12. For these examples, the F1 amplitude is plotted as a function of spatial frequency of the grating. We then fit curves through the points, using the difference-of-Gaussians model of center-surround receptive field organization (Linsenmeier et al. 1982; Rodieck 1965; Shapley and Lennie 1985; So and Shapley 1981). In this fashion, the receptive field is modeled as difference-of-Gaussians functions of opposing polarity, one for the center and one for the surround. The center Gaussian is characterized by a value for its response amplitude (K_c) and one for its diameter (R_c); likewise, the surround Gaussian can be characterized by its response amplitude (K_s) and diameter (R_s). We thus can compute these Gaussian values from the spatial tuning functions. The *bar graph insets* displayed with each set of spatial tuning curves in Figs. 11 and 12 indicate the relative change induced by parabrachial activation in each of the center and surround parameters.

It is worth noting that we fit the spatial tuning data to a

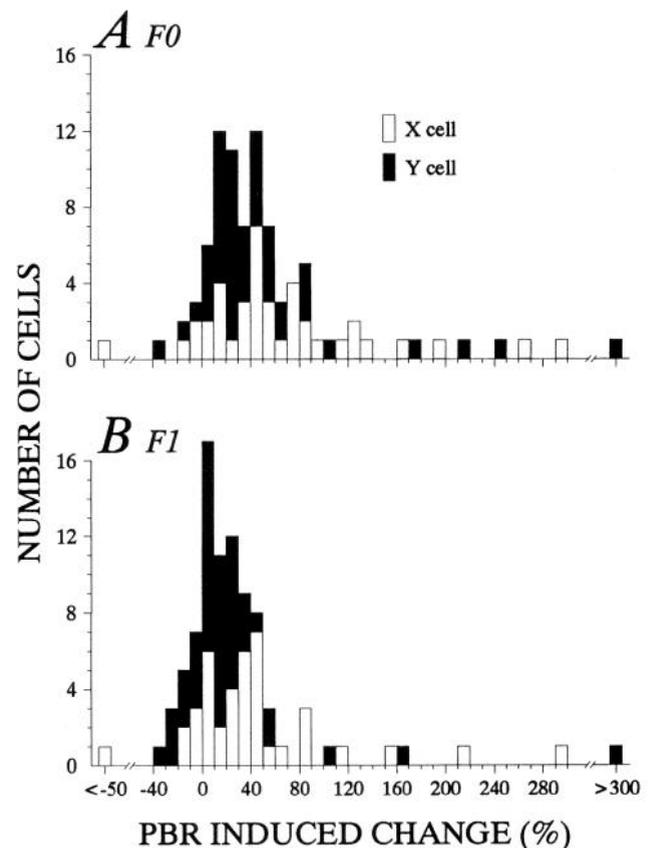


FIG. 10. Relative effect of parabrachial (PBR) train activation on visually driven responses of geniculate cells. As in Fig. 9, these data represent responses to optimal spatial frequencies. Relative changes were computed by subtracting the control response from that during parabrachial activation and dividing this difference by the control response. A: F0 values. B: F1 values.

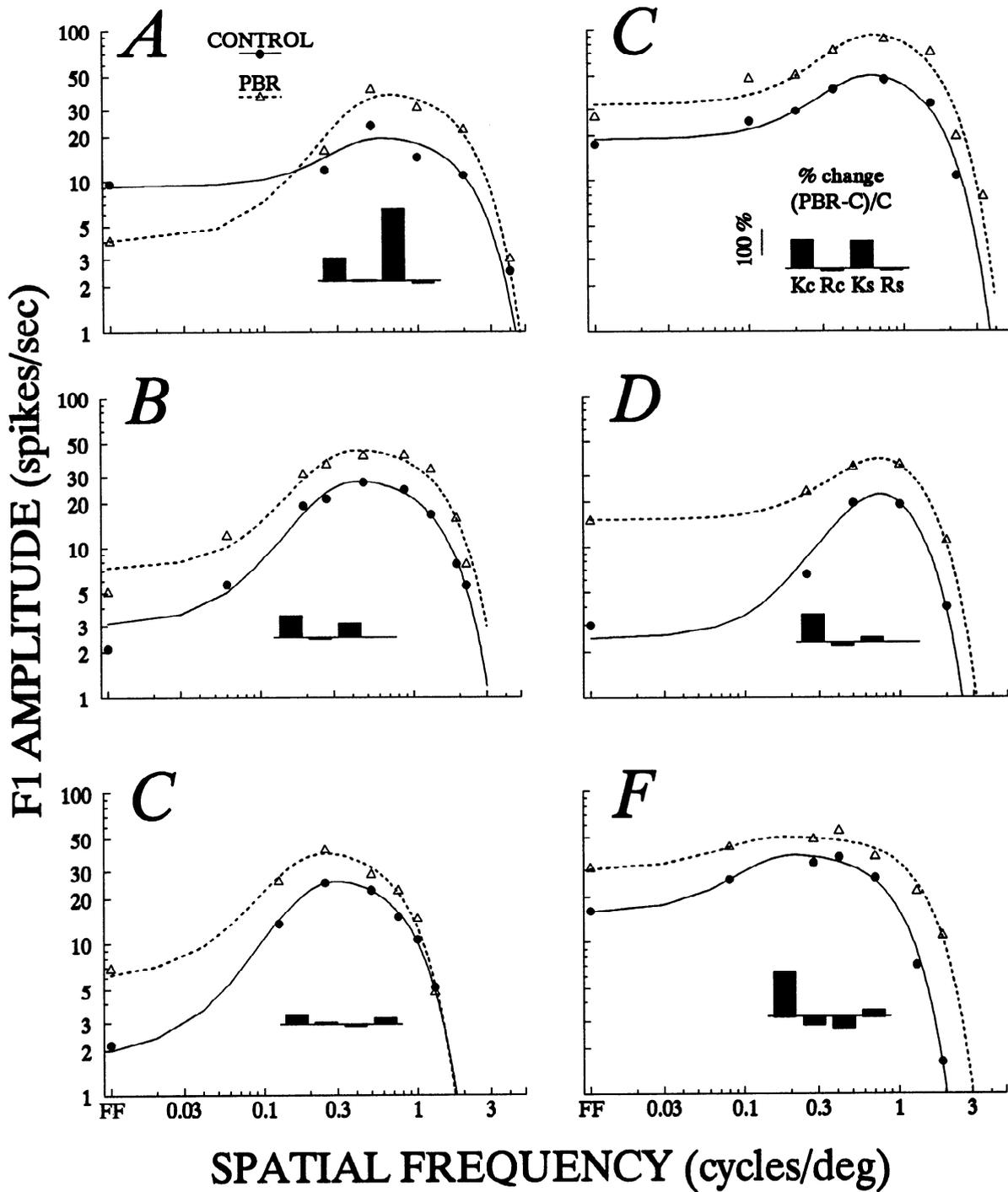


FIG. 11. Representative examples of spatial tuning curves for 6 geniculate X cells, obtained before and during parabrachial train activation. Curves drawn through the data points represent the best-fit, difference-of-Gaussians functions. *Inset bar graphs*: percentage change of the 4 difference-of-Gaussians parameters: center sensitivity (K_c), center radius (R_c), surround sensitivity (K_s), and surround radius (R_s) (see text for details). Percent change was computed as described in Fig. 10.

difference-of-Gaussians model both from linear values of frequency and response (linear fit) and from the logarithms of the response versus linear frequency values (semilogarithmic fit). Traditionally the linear fit has been used (e.g., Enroth-Cugell and Robson 1966; Linsenmeier et al. 1982; So and Shapley 1981). Recently, however, Norton et al. (1989) argued for the semilogarithmic fit, because the variance is roughly equal across spatial frequencies when it is

plotted on a logarithmic axis. The two fits often yielded dissimilar difference-of-Gaussians parameters for individual cells. However, the main observation from our *population* of X and Y cells regarding effects of parabrachial activation on these parameters was essentially the same regardless of whether linear or semilogarithmic fits were used. For simplicity, the remainder of this paper is concerned only with analyses from the linear fits.

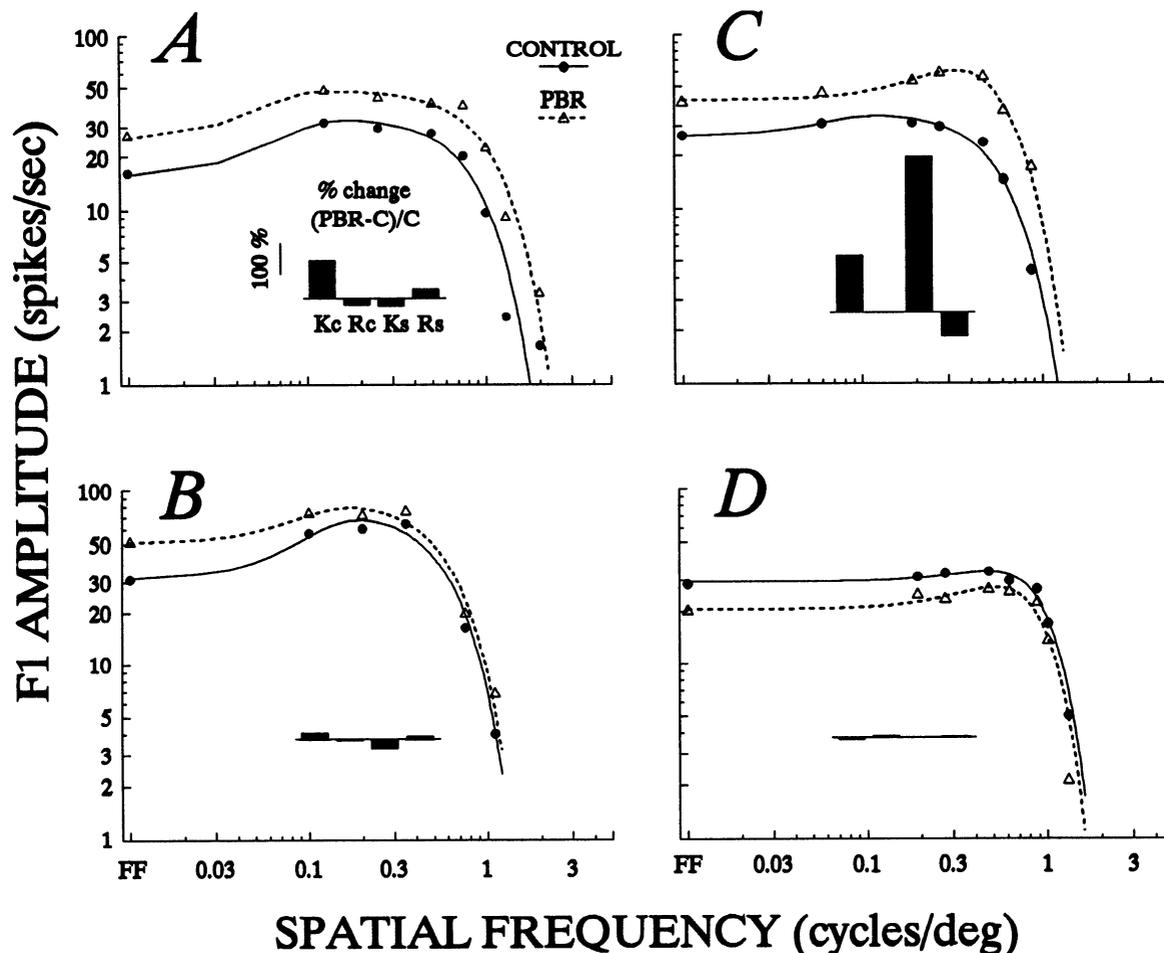


FIG. 12. Representative examples of spatial tuning curves for 4 geniculate Y cells, obtained before and during parabrachial train activation. FF on the abscissa represents the condition when the full field on the monitor was homogeneously modulated. Conventions are as in Fig. 11.

MODELING EFFECTS OF PARABRACHIAL ACTIVATION ON DIFFERENCE-OF-GAUSSIANS PARAMETERS. As a guide to interpreting effects of parabrachial activation on difference-of-Gaussians parameters, Fig. 13 shows the consequence of varying each of these parameters on spatial tuning. Note that only varying center parameters, particularly R_c , has an effect on spatial resolution. Also, while varying any of these parameters affects responsiveness to low spatial frequencies, varying center parameters affects these responses more than varying surround parameters does.

EFFECTS OF PARABRACHIAL ACTIVATION ON CENTER PARAMETERS, K_c AND R_c . Note that, for most examples shown in Figs. 11 and 12, parabrachial activation generally increased K_c , but effects on other parameters were much more variable. Figure 14 summarizes the difference-of-Gaussians parameters for all the X and Y cells studied. Overall, K_c was increased by parabrachial activation in 33 of the 39 X cells and 35 of the 44 Y cells ($P < 0.001$ for both groups on a binomial test). Most cells with increased K_c showed an increase in the modulated (F1) response at all spatial frequencies. A few cells showed broadband inhibition at all spatial frequencies, and these showed a reduction in K_c ; an example is shown in Fig. 12D. Parabrachial activation had little effect on R_c ($P > 0.05$).

Center strength is the integral of the center Gaussian function and, because the function is symmetrical around the peak, center strength is proportional to the product of K_c and the square of R_c (Enroth-Cugell and Robson 1966; Irvin et al. 1993). Figure 15A shows the distribution of center strengths before and during parabrachial activation. We found that parabrachial activation increased center strength in 30 of 39 X cells and 34 of 44 Y cells ($P < 0.001$ for both groups on a binomial test). This can largely be explained by the increase induced in K_c , because R_c was little affected.

EFFECTS OF PARABRACHIAL ACTIVATION ON SURROUND PARAMETERS, K_s AND R_s . In terms of the overall populations of X and Y cells, there was no clear tendency for parabrachial activation to affect the individual surround parameters in one particular direction (see Fig. 14). However, this is not because parabrachial activation was generally without effect on individual cells, but rather because it affected many cells by reducing K_s or R_s and other cells by increasing these parameters. In other words, parabrachial activation proved much more variable in its effects on individual surround parameters compared with center parameters, something that seems particularly evident for Y cells. This impression is supported by an analysis of variance (F tests) of relative effects of parabrachial activation: for X cells, effects on K_s

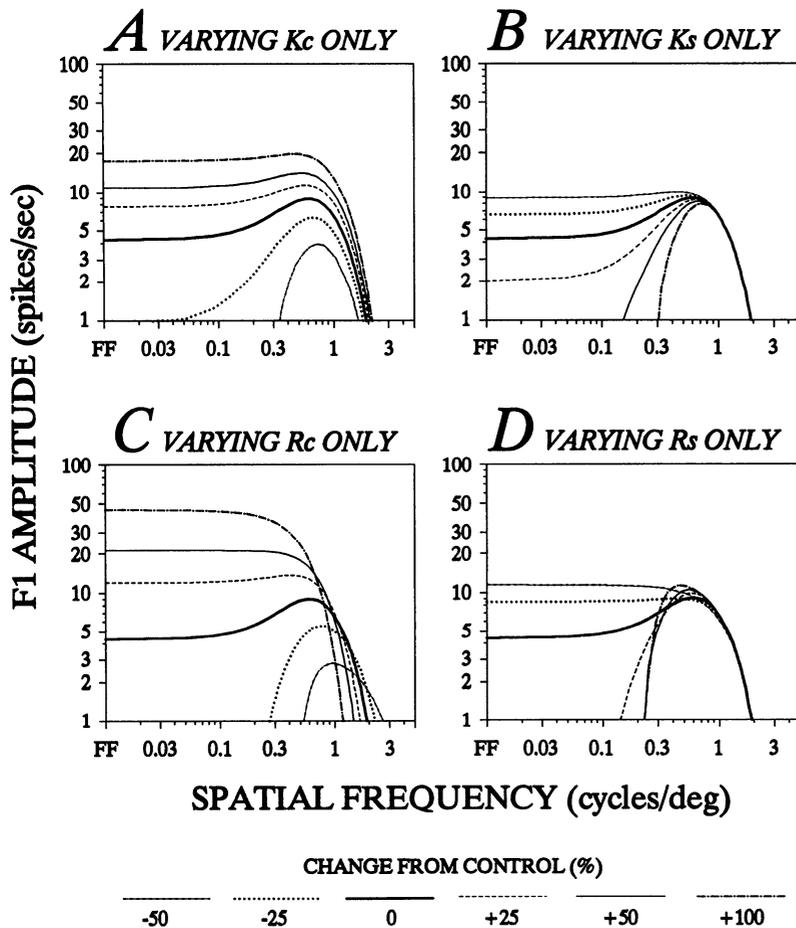


FIG. 13. Effect of varying individual difference-of-Gaussians parameters on spatial tuning. Thick, solid curve in each panel serves as a reference. The other curves reflect the effect of increasing or decreasing a single difference-of-Gaussians parameter by the indicated amount.

were more variable than those on K_c ($P < 0.01$), and effects on R_s were more variable than those on R_c ($P < 0.05$); likewise, for Y cells, effects on K_s were more variable than those on K_c ($P < 0.001$), and effects on R_s were more variable than those on R_c ($P < 0.001$). Another measure of this variability is the lack of correlation between any surround parameter and any other surround or center parameter ($r < 0.2$ and $P > 0.1$ for each of these correlations). We conclude from this that the effects of parabrachial activation on the receptive field centers of geniculate cells differed from those on the surrounds.

Surround strength can be determined in the same fashion as center strength (see above) and is thus proportional to the product of K_s and the square of R_s . Interestingly, despite the variability of parabrachial effects on individual surround parameters, Fig. 15B shows that overall, parabrachial activation consistently increased surround strength. This was true for 30 of 39 X cells ($P < 0.001$ on a binomial test) and 29 of 44 Y cells ($P < 0.02$ on a binomial test). One fairly consistent effect of parabrachial activation is thus to increase both center and surround strength.

Although the strength of both the receptive field center and surround was increased by parabrachial activation, the extent of effect on the center was typically unrelated to the effect on the surround. This is illustrated in Fig. 16, which shows the ratio of surround strength to center strength ($K_s \cdot R_s^2 / K_c \cdot R_c^2$) in the control and stimulation conditions.

The strength of the receptive field center is greater than that of the surround, resulting in ratios < 1.0 . In both the control and brain stem stimulation conditions, X cells have a higher ratio than Y cells (medians: 0.67 vs. 0.53 for the control condition and 0.70 vs. 0.47 for the stimulation condition; $P < 0.001$ for both comparisons on binomial tests). The dashed line indicates a slope of 1.0 (i.e., no change in the ratio). Although the ratios for many cells fall near this line, indicating a proportionate change in the strengths of the center and surround, the ratios of many other cells are well above or below the line, indicating a relative increase or decrease in the strength of the surround. For example, Figs. 11A and 12C exemplify large increases in this ratio (37% and 54%, respectively) and Figs. 11D and 12B exemplify large decreases (30% and 41%, respectively).

The cells clustered at the origin did not exhibit reduced responses to low spatial frequencies (i.e., had no low-frequency rolloff) and thus do not have a detectable surround. This results in a ratio of 0. The cells extending out from the origin along the abscissa are cells that exhibited a low-frequency rolloff in the control condition, but not during parabrachial activation. Examples of such cells are described further below and illustrated in Fig. 17.

DIFFERENCE BETWEEN X AND Y CELLS. As expected from prior studies (e.g., So and Shapley 1981), before parabrachial activation, each of the parameters is significantly different between cell types ($P < 0.001$, Mann-Whitney U test for

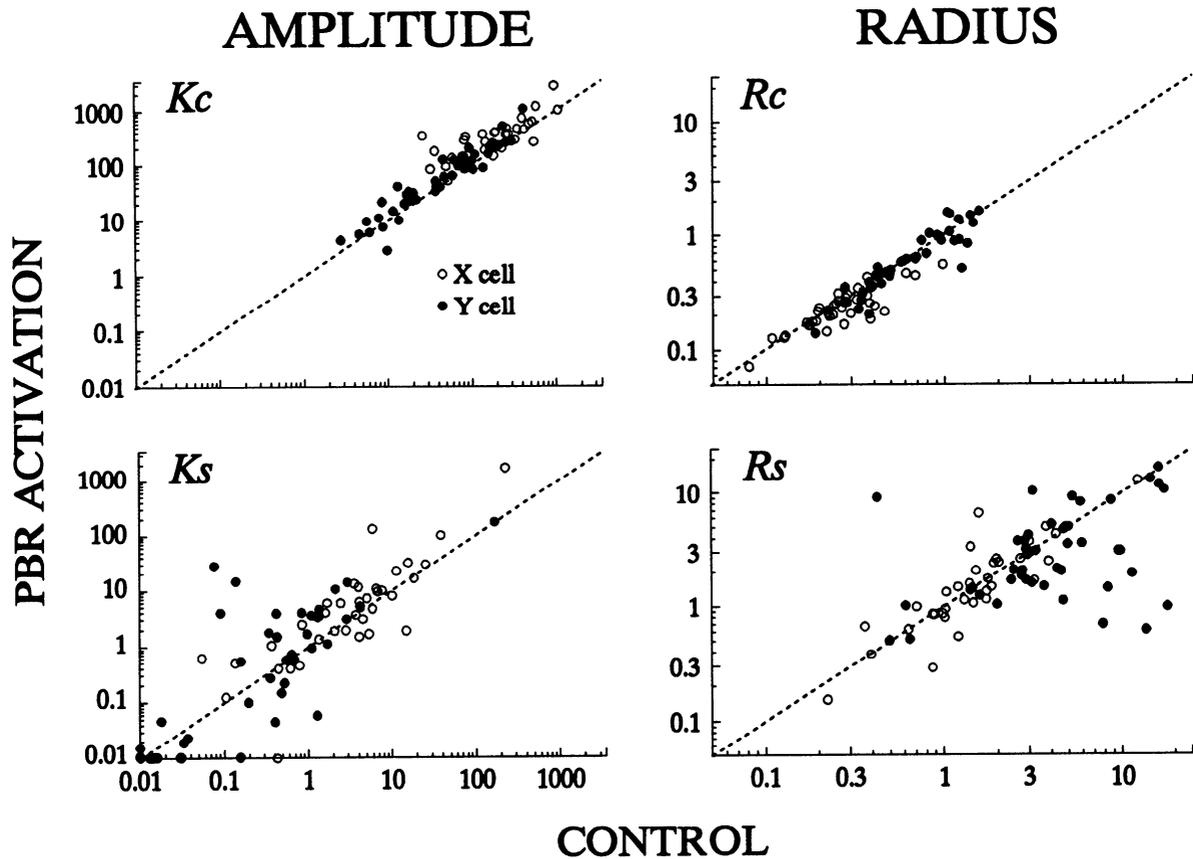


FIG. 14. Summary of the effects of parabrachial activation on the 4 difference-of-Gaussians parameters for geniculate cells. Diagonal dashed line: slope = 1, representing no effect.

each comparison). Thus, compared with X cells, Y cells have smaller K_c values, larger R_c values, smaller K_s values, and larger R_s values. In other words, both the center and surround of X cells are more sensitive and smaller than those of Y cells. During parabrachial activation, the same differences between X and Y cells are maintained ($P < 0.001$, Mann-Whitney U test for each comparison). However, it seems worth noting that the relative increase induced in K_c is greater for X cells ($28 \pm 41\%$) than for Y cells ($16 \pm 47\%$) ($P < 0.05$, Mann-Whitney U test).

UNUSUAL EXAMPLES OF EFFECTS OF PARABRACHIAL ACTIVATION ON SPATIAL TUNING. Six of the Y cells showed an unusual interaction between parabrachial activation and spatial tuning. An example is illustrated in Fig. 17A. Relative to the control response, the visual response during parabrachial activation was enhanced at low spatial frequencies and reduced at high spatial frequencies. For all six Y cells, this reflected a decrease in both K_c and K_s but a greater decline in K_s . One might make two related predictions from these spatial tuning data regarding the effects of parabrachial activation: first, that a small spot limited to the less sensitive receptive field center would evoke a smaller response; and second, that a larger spot of light would provide a better response, because although K_c is reduced, the strength of the surround, which normally attenuates responses to larger stimuli, is reduced even more. Figure 17B shows just such effects for another Y cell; this illustrates its responses to light flashes with and without a burst of parabrachial activa-

tion 100 ms before light onset. When a small spot of light is limited to the receptive field center, parabrachial activation produces a reduced visual response. In contrast, presentation of full-field illumination results in the opposite effect; now parabrachial activation results in an increase in the response.

SUMMARY. Figure 18 summarizes the effects of parabrachial activation on the receptive field structure of geniculate cells. These curves include data only from those cells showing an increase in center amplitude during parabrachial activation. Presumably these are relay cells, because, as stated above, the cells that were inhibited by parabrachial activation may have been interneurons. Figure 18, A and C, shows the average spatial tuning curves of X and Y cells. Both cell types exhibit an increase in response at all spatial frequencies during parabrachial activation. Figure 18, B and D, shows the predicted line weighting functions of X and Y cells derived from the spatial tuning curves. The weighting functions clearly illustrate the expected differences between X and Y cells that are documented in Fig. 14. That is, compared with Y cells, X cells have narrower, more responsive receptive field centers and stronger inhibitory flanks. During parabrachial activation, both X and Y cells exhibit the greatest increase in response at the center of their receptive fields, which is consistent with our observation that the response amplitude of the receptive field center is significantly increased. Although the heights of the line weighting functions increase, there is little change in their width, and the inhibitory flanks are maintained during parabrachial activation.

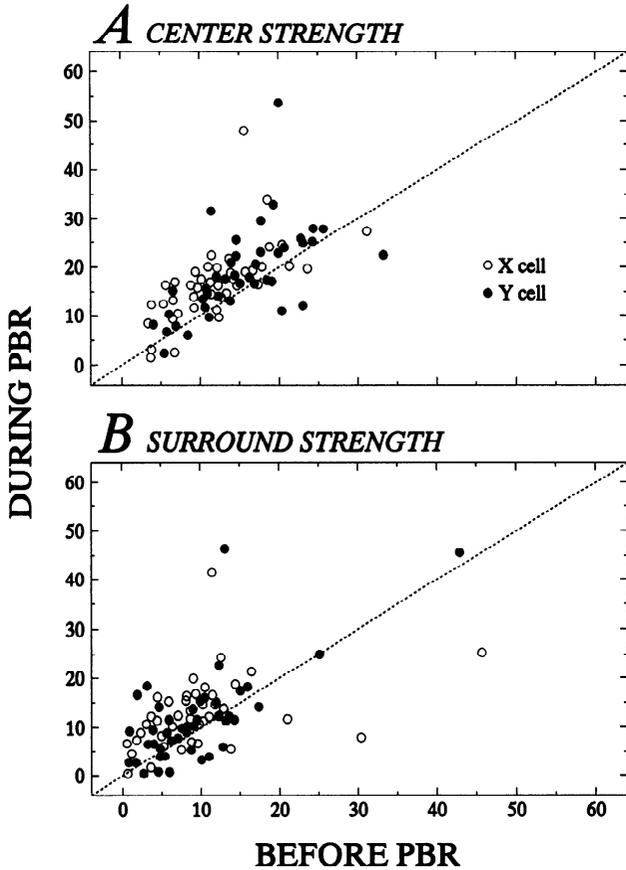


FIG. 15. Effect of parabrachial activation of the relative strength (response amplitude \cdot radius²) of the receptive field center and surround of geniculate cells. Diagonal dashed line: slope = 1, or no effect. *A*: effect on centers. *B*: effect on surrounds.

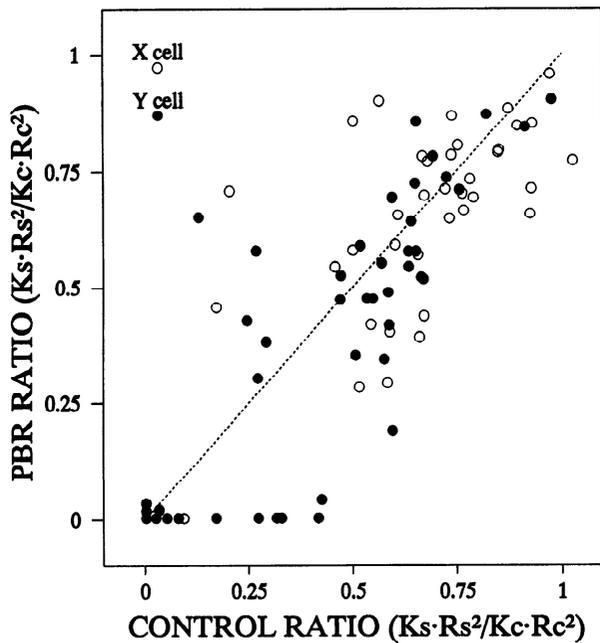


FIG. 16. Scatterplot showing ratio of surround strength to center strength before and during parabrachial activation. Dashed line: slope = 1.0, or no change in the ratio.

DISCUSSION

We studied the effects of parabrachial activation on receptive field organization of geniculate cells. To do this we acquired spatial frequency tuning curves to examine the center and surround components of these receptive fields before and during parabrachial activation. Such activation enhanced the responses of most geniculate cells, and the degree of this enhancement depended on spatial frequency. Application of a difference-of-Gaussians model revealed that the main effect of parabrachial activation on geniculate cells was an increase in both center and surround strengths. In terms of the individual Gaussian components for response amplitude (K_c and K_s) and radius (R_c and R_s), parabrachial activation produced a fairly consistent elevation of K_c with less predictable effects on the other individual components. Despite this unpredictability, increases in response amplitude more than offset decreases in radius (and vice versa) among most cells,

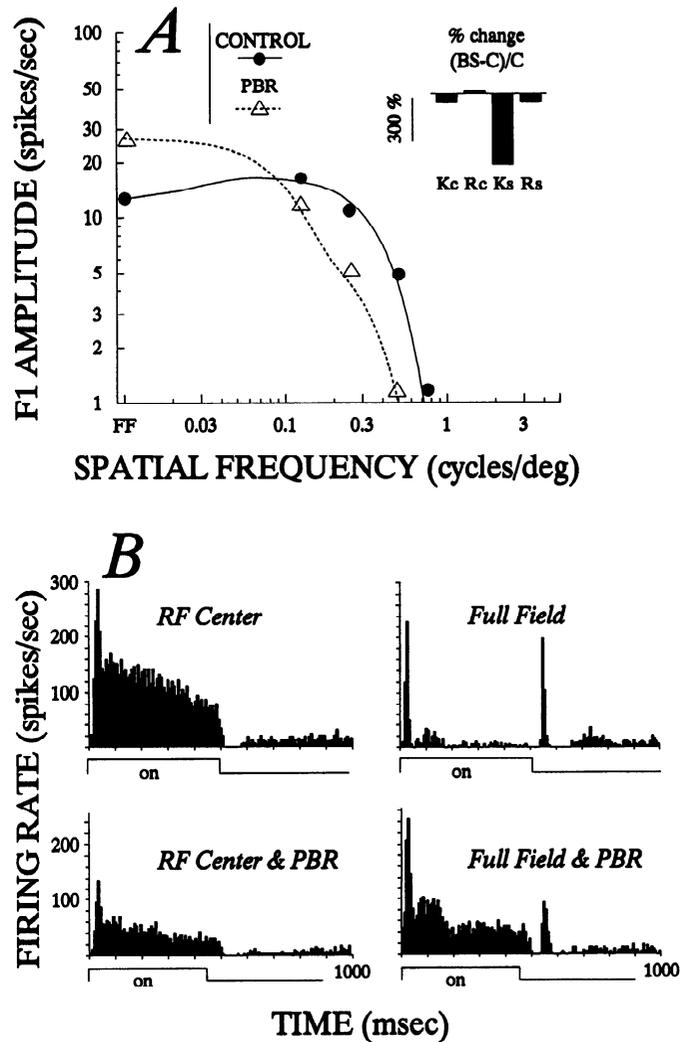


FIG. 17. Examples of unusual effects of parabrachial activation on visual responses for 2 Y cells. *A*: spatial tuning curves for 1 Y cell. Parabrachial train activation produced an enhancement of the response at low spatial frequencies and a decrement at higher spatial frequencies. Conventions are as in Fig. 11. *B*: another Y cell for which PBR 200 ms before spot onset produced a decreased response to a small light spot restricted to the receptive field center (left histograms) but enhanced the response to an FF stimulus (right histograms).

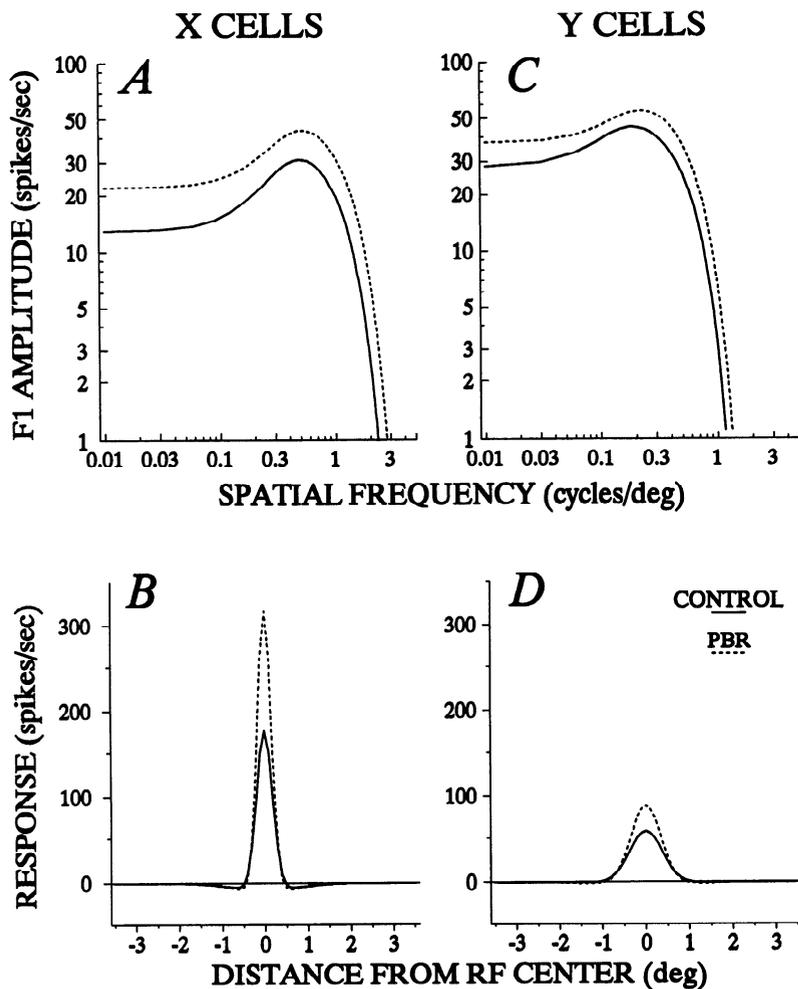


FIG. 18. Summary of the effects of parabrachial activation on the spatial receptive fields of presumed geniculate relay cells. *A* and *C*: average spatial tuning curves of X and Y cells. *B* and *D*: corresponding line weighting functions derived from the curves in *A* and *C*.

so that center and surround strengths increased for most cells. Finally, because responses of retinal axons were insensitive to parabrachial activation, the effects that we describe must result from neural processing central to the optic tract and most likely involve circuitry within the lateral geniculate nucleus.

We have interpreted our results chiefly in terms of the effects of parabrachial activation on retinogeniculate transmission. Our assumption is that the vast majority of cells we recorded were indeed relay cells and that we thus observed effects on the relay of retinal information to cortex. However, although roughly 75% of the cells in the lateral geniculate nucleus are relay cells, the remaining 25% are interneurons. We assume that our cell sample includes interneurons, but without specialized techniques, which we did not employ, we could not reliably distinguish between interneurons and relay cells. However, given the relatively small size of interneurons (Fitzpatrick et al. 1984; Montero and Zempel 1985), we assume the actual number sampled with our electrodes was <25% and probably <10%, consistent with other studies performed in our laboratory that allowed identification of interneurons (e.g., Friedlander et al. 1981; Sherman and Friedlander 1988). Although identification of possibly different effects on relay cells and interneurons is potentially important and must await further study, the fact

that the large majority of our sample responded to parabrachial activation in a consistent fashion (e.g., the increases in center and surround strengths) makes it reasonable to assume that this reflects the pattern of effects on relay cells.

Mechanisms of parabrachial activation

It seems likely that ACh operating through various muscarinic and nicotinic receptors plays a major role in the effects we have described. Considerable anatomic evidence indicates that the largest ascending pathway from the brain stem to the lateral geniculate nucleus emanates from cholinergic neurons in the parabrachial region (DeLima and Singer 1987; Fitzpatrick et al. 1989; Smith et al. 1988). Our stimulating electrodes were placed at the rostral end of the parabrachial region to activate the cholinergic cell bodies there as well as the ascending axons of more caudal cholinergic neurons; we thus positioned these electrodes to stimulate these cholinergic parabrachial cells maximally. Furthermore, others have shown that the effects of parabrachial activation can be reduced or even blocked by cholinergic antagonists (e.g., Francesconi et al. 1988; Hu et al. 1989). Also, application of ACh onto geniculate cells *in vivo* produces an enhancement of responses that is consistent with that produced by parabrachial activation (Eysel et al. 1986; Francesconi

et al. 1988; Hu et al. 1989; Kemp and Sillito 1982; Sillito et al. 1983).

Although ACh seems to be a major transmitter involved in the parabrachial effects we have described, other ascending brain stem projections and other neuromodulators or peptides may also be involved. Ascending axons passing through the parabrachial region from caudal brain stem regions to the lateral geniculate nucleus may also have been activated, and these would have used other neurotransmitters, such as noradrenaline or serotonin (e.g., DeLima and Singer 1987). Also, cells of the parabrachial region are not homogeneously cholinergic, and even cholinergic cells seem to colocalize other neuroactive substances, such as various peptides and nitric oxide (Bickford et al. 1993; Vincent et al. 1983, 1986). These very likely contribute to the effects we have reported. However, because cholinergic axons dominate brain stem input to the cat's lateral geniculate nucleus (DeLima and Singer 1987; Fitzpatrick et al. 1989) and because relatively little is known about the pharmacological actions of the other neuroactive substances (see, however, McCormick 1992; Pape and Mager 1992), we will focus on what can be inferred from our knowledge of ACh with respect to the cat's lateral geniculate nucleus.

The parabrachial effects we observed are probably the result of both direct and indirect innervation of geniculate cells. Anterograde tracing and immunohistochemical studies (Beaulieu and Cynader 1992; Cucchiari et al. 1988; DeLima et al. 1985; Raczkowski and Fitzpatrick 1989) show that parabrachial axons and cholinergic terminals synapse directly onto geniculate relay cells, interneurons, and perigeniculate cells, the latter two cell groups being local, inhibitory, GABAergic cells. In vitro studies indicate that, in the cat, geniculate relay cells are excited directly by ACh via both nicotinic and muscarinic receptors (McCormick and Prince 1987). Activation of the nicotinic receptors produces a fast, brief depolarization by increasing a conductance to cations. Activation of the muscarinic receptors in relay cells produces a much slower, more prolonged depolarization by blocking a K^+ conductance. Some relay cells also can be directly hyperpolarized via a muscarinic receptor that gates an increase in a K^+ conductance. In contrast, geniculate interneurons and perigeniculate cells exhibit only the muscarinic-mediated hyperpolarization in response to ACh (McCormick 1991; McCormick and Pape 1988; McCormick and Prince 1986). Consistent with this pharmacology of interneurons and perigeniculate cells is the observation that the spontaneous activity of both cell types is suppressed in vivo by parabrachial activation (Ahlsen et al. 1984; Francesconi et al. 1988; Murphy et al. 1994). It is not clear what combination of cholinergic receptors and direct and indirect effects contributes to the elevated firing caused by train stimulation that we used for most of this study.

Effects of parabrachial activation on visual responses

A major rationale for our study was to present a clearer picture of the effects of parabrachial activation on receptive field properties of geniculate relay cells. Prior investigations of this problem were not able either to separate generalized changes in excitability from more specific changes in the depth of modulation to visual stimuli or to detect changes

in receptive field structure. We used a different approach involving linear systems analysis with the use of a difference-of-Gaussians model of center and surround strengths to describe receptive field structure. We were therefore able to distinguish changes in overall responsiveness evoked by visual stimuli from changes in modulation depth, and we could relate this to separate effects on the receptive field center and surround.

GENERAL EFFECTS ON RESPONSIVENESS. The most robust effect of parabrachial activation on the visual responses of geniculate cells was the increase in the amplitude of the response. This effect could take somewhat different forms. Some cells exhibited rather little response to the visual stimulus in the control condition and yet revealed a vigorous visual response during parabrachial activation (e.g., Fig. 5, *A*, *B*, and *F*). These are extreme examples of the gating of retinogeniculate transmission: before parabrachial activation these geniculate cells relay little retinal information to cortex, but during activation the relay is much stronger. For most geniculate cells the enhancement of the relay function was subtler but still quite clear (e.g., Fig. 5, *D* and *G-I*). For a minority of cells the enhancement in response appeared as an increase in the background activity, with little or no effect on the modulated response (e.g., Fig. 5*C*). It is difficult to determine the significance of such an effect, especially when so few cells show the effect. However, the increase in overall firing might help to bring postsynaptic cortical cells, most of which have very low spontaneous activity, to firing threshold during the crests of modulated activity. This, too, would enhance the ability of geniculate relay cells to transmit retinal information to cortex. Therefore increased parabrachial activity seems to enhance the relay of retinal signals through the lateral geniculate nucleus for most relay cells, which is consistent with a role for the parabrachial region in mechanisms of enhanced arousal or attention.

Finally, a different and distinct response in a minority of cells was a reduced firing amplitude in response to parabrachial activation (e.g., Fig. 5, *E* and *J*). If these examples come from relay cells, then under some circumstances parabrachial activation can serve to impede retinogeniculate transmission, at least for some cells. However, another possibility seems more likely. As discussed above, interneurons probably represent a minority of our sample. Application of ACh inhibits interneurons, so it is reasonable to conclude that parabrachial activation will likewise reduce the responsiveness of interneurons (see also Ahlsen et al. 1984). Therefore it seems plausible that the examples shown in Fig. 5, *E* and *J*, represent interneurons and not relay cells. The confirmation of this hypothesis will require further study to distinguish between relay cells and interneurons.

EFFECTS ON CENTER AND SURROUND COMPONENTS OF THE RECEPTIVE FIELD. We relied chiefly on the difference-of-Gaussians model to determine differential effects of parabrachial activation on receptive field centers and surrounds. To be used generally and precisely to predict responses to visual stimuli, this model requires assumptions of linearity of response (Shapley and Lennie 1985) that are not completely met by the responses of most geniculate cells either before or during parabrachial activation. Nonetheless, the model fits our data well, and it can still be used to examine

receptive field structure (e.g., Shapley and Lennie 1985; So and Shapley 1981). Application of the difference-of-Gaussians model seems a reasonable first step in analyzing the effects of parabrachial activation on receptive field properties.

The most consistent effect of parabrachial activation we observed was an increase in both center and surround strength ($K_c \cdot R_c^2$ and $K_s \cdot R_s^2$, respectively). Among individual parameters, K_c was most consistently enhanced, and this enhancement was greater in X cells than in Y cells. Little effect was seen on center radius, and surround amplitude and radius were both quite variably affected even though surround strength was reliably enhanced. However, there was significantly more variability seen among our cell sample in the increase in surround strength than for the increase in center strength. Our results are consistent with prior reports that the strengths of the receptive field center and surround increase, whereas there is no change in the width of the receptive field, during arousal (Livingstone and Hubel 1981) or on application of ACh (Eysel et al. 1986; Sillito et al. 1983).

Recently, Hartveit et al. (1993) examined the effects of parabrachial stimulation on the spatial receptive field properties of geniculate cells. For the visual stimulus, Hartveit et al. (1993) used thin slits of light that were flashed on and off at different positions across the receptive field. Our findings agree in part with their conclusions in that the strength of the receptive field center increases with parabrachial activation. However, Hartveit et al. (1993) reported an increase in the breadth of the receptive field center, which we and others have not reported. A concern regarding the results of Hartveit et al. (1993) is their stimulation paradigm. They activated the parabrachial region either with a burst of electrical pulses before onset of the light slit or with a train of pulses during most of the visual presentation. The visual response, and its change by parabrachial stimulation, was measured by counting the number of spikes during the visual presentation. However, as we have documented here and others have reported (e.g., Francesconi et al. 1988; Humphrey and Saul 1992; Singer 1977), parabrachial activation elevates the responses of geniculate cells in the absence of visual stimulation. Thus, in the paradigm used by Hartveit et al. (1993), it is difficult to distinguish a change in the visual response from the effects of simply activating the parabrachial region.

The pattern of effects on center and surround components of the receptive field, which may seem puzzling at first glance, is consistent with many observations made from prior studies of neurons in the lateral geniculate nucleus. Many of these studies have emphasized the close similarities between the receptive field structure of geniculate cells and that of their retinal afferents. Only subtle changes were detected at geniculate levels, primarily in the form of enhanced antagonism of the center by the surround (Cleland et al. 1971b; Hubel and Wiesel 1961). Most explanations of geniculate receptive field properties combine two features of geniculate circuitry. First, for the most part, receptive fields of geniculate cells simply reflect those of their retinal afferents, especially because there is very little convergence in retinogeniculate connections. Second, local GABAergic in-

terneurons and/or perigeniculate cells provide inhibitory inputs to relay cells pooled over a relatively large area, and this contributes to the surround. This means that center properties are largely a reflection of retinogeniculate transmission, whereas the surround reflects both retinogeniculate transmission and the influence of local inhibitory inputs. Parabrachial activation can influence the receptive field center and surround in ways that are consistent with our results.

For almost all of the geniculate cells, parabrachial activation increased the modulated response at all spatial frequencies. This is consistent with an induced enhancement of the strength of the receptive field center, which results primarily from an increase in K_c . These effects on the center presumably reflect an increase in the efficiency of the retinogeniculate synapse. Previous *in vivo* studies have shown that the visual responses of geniculate cells are reduced from that of their retinal input (Cleland and Lee 1985; Cleland et al. 1971a,b; Mastrorade 1987), so the retinogeniculate transmission is normally less than optimal. Several mechanisms may account for the improvement of retinogeniculate transmission produced by parabrachial activation. Both parabrachial activation and ACh application depolarize thalamic relay cells directly and produce an increase in their input resistance (see above; see also Curró Dossi et al. 1991; Deschênes and Hu 1990; McCormick and Prince 1987). Excitatory postsynaptic potentials (EPSPs) are enhanced by a higher input resistance, and a depolarized cell requires a smaller depolarization to reach threshold for firing; thus parabrachial activation would allow many otherwise subthreshold EPSPs to evoke firing. Furthermore, the membrane depolarization caused by parabrachial activation would inactivate certain conductances, such as the low-threshold Ca^{2+} spike and an outward K^+ current similar to I_A (Jahnsen and Llinás 1984; McCormick 1991, 1992), and these conductances can diminish the efficiency of retinogeniculate transmission. Depolarization will also enhance retinogeniculate transmission supported by activation of *N*-methyl-D-aspartate receptors (Scharfman et al. 1990; Sillito et al. 1990).

We also observed that parabrachial activation caused an increase in the strength of the receptive field surround. This at first seems contradictory with the presumed disinhibitory effect of parabrachial activation. That is, if interneurons and/or perigeniculate cells contribute to the receptive field surround of geniculate cells, how could the surround be *increased* when the activity of interneurons and perigeniculate cells is *suppressed* by parabrachial activation? Recall from the above discussion that much of the receptive field surround in geniculate neurons is inherited from the retinal input. Thus any of the factors noted in the prior paragraph that enhances retinogeniculate transmission should enhance center and surround strengths together. This is because a proportionate increase in the response of a geniculate cell to all spatial frequencies reflects a proportionate increase in both K_c and K_s . However, the contribution to the surround of interneurons and perigeniculate cells allows a second route by which parabrachial activation may affect surround properties. Thus parabrachial activation could alter the strength of the inhibitory input arising from these GABAergic cells. Parabrachial activation could also affect the phase of this inhibitory input, and variations in the phase lag between the center and surround responses can dramati-

cally affect the overall effectiveness of the surround (e.g., Kaplan et al. 1979). We found no evidence for such a relative phase shift for nonlagged cells. However, this possibility should be tested for lagged cells, which exhibit a large advance in the relative phase of their response during parabrachial activation. This overall phase shift could well reflect a different phase effect on center and surround. The additional and assorted contribution of interneurons and perigeniculate cells may be the cause of the greater variation seen in surround versus center parameters as a result of parabrachial activation.

There is yet further cause for variability here. For instance, because ACh and parabrachial activation generally inhibit interneurons and perigeniculate cells, one would expect their contribution to surround parameters to be somewhat diminished. However, although parabrachial activation consistently suppresses the spontaneous activity of perigeniculate cells, it may suppress or enhance perigeniculate responses to visual stimuli, depending on the spatiotemporal properties of the visual stimulus (Francesconi et al. 1988; Funke and Eysel 1993; Murphy et al. 1994). This variability, in turn, may be due to offsetting effects of parabrachial activation on these perigeniculate cells: there is a direct inhibitory effect plus an indirect excitatory effect, the latter due to increased activity of inputs from geniculocortical axons (and possibly, from corticogeniculate axons). In any case, receptive fields of perigeniculate cells are variably affected by parabrachial activation, and this translates to an even wider variety of effects on the receptive field surrounds of geniculate cells. There is no well-documented study of the effects of parabrachial activation on the receptive fields of interneurons, but interneurons add yet another potential source of variability contributing to the receptive field surround of geniculate relay cells. Nevertheless, these phenomena are consistent with our observation that parabrachial activation produces more variable effects on surround parameters than on center parameters for geniculate cells.

Differences between effects on X and Y cells

We found that parabrachial activation increased the K_c of X cells more than that of Y cells. This is consistent with previous findings that such activation affects X cells more than Y cells (e.g., Francesconi et al. 1988; Fukuda and Stone 1976) and suggests that the retinogeniculate synapse of X cells is more effectively gated by parabrachial inputs than that of Y cells. A plausible anatomic substrate of this X-Y difference is the synaptic triad, whereby a retinal terminal forms synapses with a dendritic appendage of a relay cell and with a dendritic terminal (known as an F2 profile) of an interneuron. The F2 profile completes the triad by forming a synapse with the appendage of the relay cell. Because F2 profiles are GABAergic (Montero 1986; Montero and Singer 1985), they are presumably inhibitory and are ideally situated to suppress the retinogeniculate synapse. Most of the retinal input to geniculate X cells is delivered through these triadic arrangements, and relatively little of the retinal input to geniculate Y cells is triadic (e.g., Hamos 1990; Hamos et al. 1985, 1987; Wilson et al. 1984). Cholinergic and/or parabrachial terminals synapse on the F2 profiles (Cucchiari et al. 1988; DeLima et al.

1985; Raczkowski and Fitzpatrick 1989), which contain the m2 subtype of muscarinic receptor (Plummer et al. 1993) and thus are presumably inhibited by cholinergic input (e.g., Jones 1993; Noda et al. 1993). By controlling activity of the F2 terminal, parabrachial inputs may be able to affect the retinogeniculate synapse to X cells in a more powerful and direct way than is available for Y cells.

Conclusions

Parabrachial activation increases the strength of both center and surround components of receptive fields for most geniculate relay cells. The effects of parabrachial activation on the center are more consistent than those on the surround, possibly because the center effects simply reflect enhanced retinogeniculate transmission whereas the surround effects are a complex combination of enhanced retinogeniculate transmission plus an additional set of effects on local inhibitory circuits. The end result of parabrachial activation is that a more robust visual signal is relayed to cortex with a concomitant preservation of lateral inhibitory mechanisms. Preservation of the surround seems at first glance to contradict the notion that parabrachial activation inhibits the local inhibitory cells, but, as we have noted above, there are two reasons why this is not a contradiction. First, much of the surround strength is relayed across the retinogeniculate synapse, and parabrachial activation enhances retinogeniculate transmission. Second, although parabrachial activation consistently inhibits spontaneous activity of local inhibitory cells, it actually enhances responses to certain visual stimuli for many of them (Murphy et al. 1994).

The effect of increased center and surround strength can be appreciated by simple consideration of the difference-of-Gaussians model. Both Gaussian functions act as low-pass filters for spatial frequencies, but the center function responds to higher spatial frequencies. Thus increased center strength increases responses to all frequencies, whereas increased surround strength maintains the reduced responses to lower spatial frequencies. The low-frequency attenuation caused by the surround inhibition results in a relatively stronger response to high spatial frequencies, which convey detail in a visual scene. This produces an enhancement of contrast edges, a well-known example of this being Mach bands (see Cornsweet 1970).

We suggest that parabrachial activation mimics in a very crude manner what happens more physiologically when cells in the parabrachial region become more active. Such increased activity in the parabrachial brain stem region is often associated with increased arousal and attention (Singer 1977; Steriade and Llinas 1988; Steriade and McCarley 1990). It makes sense that such increased activity should lead to a more robust relay of retinal signals through the lateral geniculate nucleus along with filtering that helps to sharpen the visual image.

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