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Brain-stem modulation of the response properties of cells in the cat's perigeniculate nucleus

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Abstract

Transmission through the lateral geniculate nucleus is facilitated following activation of the cholinergic input from the brain stem, which is thought to reflect activity patterns seen during arousal. One of the underlying mechanisms is the suppression of inhibitory circuits local to the lateral geniculate nucleus. However, evidence exists that some visually driven inhibitory inputs to geniculate relay cells may be preserved or even enhanced under conditions of arousal, and during electrical activation of the parabrachial region of the brain stem. We have therefore reexamined the effect of brain-stem activation on the visual responses of one group of local inhibitory inputs to geniculate relay cells, those emanating from the adjacent perigeniculate nucleus. We recorded single perigeniculate cells in anesthetized, paralyzed cats. Axons innervating the lateral geniculate and perigeniculate nuclei from the parabrachial region of the brain stem were electrically activated, and the effect of this activation was assessed on both spontaneous and visually evoked responses. Visual stimulation consisted of sinusoidally modulated sine-wave gratings of varying spatial and temporal frequency. For the great majority of perigeniculate cells (32 of 40), brain-stem activation inhibited spontaneous activity, while one cell was excited, three showed a mixed effect and four were unaffected. Nevertheless, the responses of most cells (30 of 40) were facilitated when brain-stem activation was paired with certain spatio-temporal patterns of visual stimulation. Spatial tuning curves were constructed for 17 cells and temporal tuning curves for 14, before and during parabrachial activation. The responses of any one cell could be facilitated, unchanged, or suppressed, depending on the visual stimulus used. In some cases, this substantially modified the cell's spatial and temporal tuning properties. We conclude that activation of the brain stem disinhibits geniculate relay cells in the absence of visual stimulation, but it has the potential to enhance either the magnitude or specificity of visually driven inhibition arising from the perigeniculate nucleus.

Keywords: Perigeniculate nucleus, Thalamic reticular nucleus, Parabrachial region, Acetylcholine, Retinogeniculate transmission

Introduction

The lateral geniculate nucleus represents the thalamic relay between the retina and visual cortex. Receptive fields of geniculate cells bear a strong resemblance to those of their afferent retinal ganglion cells (Hubel & Wiesel, 1961; Cleland & Lee, 1985), and it has thus been assumed that little processing of the visual signal takes place at this level. Nevertheless, geniculate relay cells are subject to a complex pattern of synaptic influences from nonretinal sources, both extrinsic and intrinsic to the lateral geniculate nucleus (Sherman & Koch, 1986, 1990). This includes a substantial input from two populations of local inhibitory neurons that use γ-aminobutyric acid (GABA) as a neurotransmitter. One population consists of interneurons intrinsic to the lateral geniculate nucleus (Fitzpatrick et al., 1984; Montero & Zempel, 1985) while the other originates in the perigeniculate nucleus, a thin sheet of GABAergic cells that lie just dorsal to the lateral geniculate nucleus itself. The perigeniculate nucleus appears to be a subdivision of the thalamic reticular nucleus that is related to the lateral geniculate nucleus. Perigeniculate cells receive input from collaterals of relay cell axons *en route* to cortex (Ahlsén et al., 1978; Friedlander et al., 1981; Ahlsén & Lindström, 1982; Ide, 1982; Ahlsén et al., 1982; Montero, 1989), and thus constitute a recurrent inhibitory pathway (Dubin & Cleland, 1977; Montero & Scott, 1981; Lindström, 1982; Uhlrich et al., 1991).

An important nonvisual input to the lateral geniculate nucleus originates in the parabrachial region of the brain stem (Ahlsén & Lo, 1982; Uhlrich et al., 1988), from cells that are

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largely cholinergic (Kimura et al., 1981; De Lima & Singer, 1987; Smith et al., 1988). In addition to contacting relay cells, cholinergic axons contact interneurons and perigeniculate cells (De Lima et al., 1985; Raczkowski & Fitzpatrick, 1989), as do axons of known parabrachial origin (Cucchiaro et al., 1988). However, the cholinergic axons from the parabrachial region seem to have different effects on their different target neurons. Iontophoretically applied acetylcholine excites relay cells (Phillis et al., 1967; Sillito et al., 1983) through a nicotinic- and muscarinic-mediated depolarization (McCormick & Prince, 1987), while it hyperpolarizes and therefore inhibits inhibitory interneurons (McCormick & Pape, 1988) and perigeniculate cells (Godfraind, 1978; McCormick & Prince, 1986; McCormick, 1989) *via* a separate muscarinic receptor. Thus, the cholinergic input has the potential to increase the responsiveness of relay cells, both directly by excitation and indirectly by disinhibition. This pattern of effect has been confirmed by electrical activation experiments (Singer, 1973; Fukuda & Stone, 1976; Ahlsén et al., 1984; Francesconi et al., 1988). Furthermore, depolarization inactivates the low-threshold calcium conductance underlying high-frequency burst discharges in thalamic relay cells, and inhibition of the recurrent inhibitory circuit involving perigeniculate cells suppresses the generation of synchronous oscillatory activity (Steriade & Llinás, 1988; Steriade & Deschênes, 1988). Hence, the cholinergic input also has the potential to promote more faithful and more linear retinogeniculate transmission (Steriade & Llinás, 1988; Steriade & Deschênes, 1988; Lu et al., 1993). Parabrachial cells are on average most active when the animal is alert (Steriade et al., 1982). This pathway is therefore thought to be involved in the state-dependent gating of geniculate relay cell activity, and inhibition of local inhibitory circuits, including those from the thalamic reticular and perigeniculate nuclei, is thought to be an important component of its influence (Steriade & Llinás, 1988; Steriade & Deschênes, 1988; Francesconi et al., 1988).

It is thus surprising that the thalamic reticular and perigeniculate nuclei are more active in the alert animal than in the anesthetized preparation (Mukhametov et al., 1970; Steriade et al., 1986). Although consistent with the fact that other modulatory inputs facilitate these cells (McCormick, 1989; McCormick & Wang, 1991), this is difficult to reconcile with the substantial body of evidence suggesting that the cholinergic pathway suppresses their activity (Phillis et al., 1967; Dingledine & Kelly, 1977; Godfraind, 1978; Sillito et al., 1983; Ahlsén et al., 1984; McCormick & Prince, 1986; Francesconi et al., 1988). It nonetheless appears that visually driven inhibitory inputs to geniculate cells are preserved or even enhanced during arousal (Livingstone & Hubel, 1981). Furthermore, our own laboratory (Uhlrich et al., 1989) has confirmed that, for half of the geniculate cells tested, electrical activation of the cholinergic parabrachial region leads to changes in receptive-field structure compatible with an increase, rather than a decrease, in surround inhibition.

In light of this evidence, we have reexamined the effects of parabrachial activation on the visual responses of perigeniculate cells. We used the same stimulus paradigms that we previously applied to our analogous study of geniculate cells (Uhlrich et al., 1989). The results show that, in virtually all cases, spontaneous activity was indeed suppressed, as were the responses to many visual stimulus conditions. This has been reported previously by several authors (Francesconi et al., 1988; Hartveit et al., 1993), who studied only a handful of cells using a single form of visual stimulus. However, we found that the effects on visually driven activity varied with spatial and temporal frequency, leading to marked changes in the cells' tuning properties. More surprisingly, for many spatiotemporal patterns of visual stimulation, the evoked responses of perigeniculate cells were dramatically enhanced by parabrachial activation. This work has been published previously in abstract form (Murphy et al., 1989).

Materials and methods

Experiments were carried out on 11 adult cats, which were anesthetized with halothane (0.5% in a 70/30 mixture of N_2O/O_2) and paralyzed with gallamine triethiodide plus curare. We dilated the pupils by topical application of atrophine sulphate, retracted the nictitating membranes with phenylephrine hydrochloride, and fitted the corneas with contact lenses to protect the eyes and focus them on the visual stimulus. EEG, ECG, and expired air CO_2 levels were monitored continuously. Full details of our preparation and maintenance techniques have been published elsewhere (Bloomfield & Sherman, 1987; Uhlrich et al., 1991; Lu et al., 1993).

We implanted a pair of bipolar stimulating electrodes to straddle the optic chiasm at A14, L1.0-1.5, and at a depth determined by maximizing the visually evoked potential recorded from the electrodes. We then applied single shocks (50–100 μs and 150–700 μA) to activate retinogeniculate afferents. A second pair of electrodes was introduced into the midbrain parabrachial region, at stereotaxic location AP0, H1, and L1 plus L3-4. This location was identified in previous experiments to be the main source of parabrachial input to the lateral geniculate nucleus (Uhlrich et al., 1988). Since >90% of the afferents arising from that region are cholinergic (De Lima & Singer, 1987; Smith et al., 1988), this is also the only known source of cholinergic input to the lateral geniculate and perigeniculate nuclei (see also Bickford et al., 1993*b*). Correct electrode placement in the parabrachial region was confirmed prior to cementing them in place by demonstrating that the potential evoked in the lateral geniculate nucleus by optic chiasm activation could be increased by activation through the parabrachial electrodes, and it was confirmed histologically at the end of every experiment. These electrodes were then used to activate the ascending pathway to the thalamus, using positive current pulses of 50–100 μs duration and 150–700 μA amplitude. We used two basic stimulus paradigms: either a short period of high-frequency activation (four shocks at 250 Hz) which is hereafter described as "burst" activation, or prolonged trains of pulses of varying frequency and duration (5–50 Hz for 500–1200 ms) which will be referred to as "train" activation. To build the peristimulus-time response histograms from which tuning curves were constructed, we used trains of stimuli that spanned at least one whole visual stimulus cycle. This ensured both that the parabrachial stimulus period did not coincide with any one phase of the visual stimulus and that timing differences did not occur between the different variable states.

We made extracellular recordings from single units, using electrodes filled with Pontamine sky blue (2% w/v) in 0.5 M sodium acetate, bevelled to an impedance of 5–10 MΩ. Units were identified as perigeniculate cells if they were located above the lateral geniculate nucleus, had poorly localized, large, and often binocular receptive fields, and expressed a variable latency to optic tract activation in the range of 1.6–3.2 ms (Wrobél &

Tarnecki, 1984). The location was confirmed by subsequent penetration and recording in geniculate laminae A and A1. The geniculate cells recorded at these times were found to be stable and responsive, with normal visual response properties, confirming that the preparation was healthy. In addition, 27 of the 43 recording sites were identified by histological reconstruction of electrode tracks marked by strategically placed dye spots.

Each receptive field was first plotted on a frontal tangent screen, and a cathode ray tube subtending 12 deg or 24 deg of visual angle was positioned in front of the animal and centered over the dominant eye's receptive field. The other eye was occluded. We then stimulated the cell with a series of drifting sinusoidal gratings, of differing spatial and temporal frequency, or with a sinusoidally modulated, full-field display. Average luminance of the display was 40 cd/m^2, and the contrast was 0.6. Each stimulus was repeated between 10 and 55 times. To obtain spatial and temporal frequency tuning curves, stimuli were presented in a block random fashion; that is, all of the stimulus conditions were presented only once, in a randomly interleaved sequence, before any stimulus was repeated. Each presentation included a control period and a period of parabrachial activation, followed by a recovery period. Hence the control and experimental data were paired on a trial-by-trial basis, and averaged over a large number of independent trials. Under these circumstances, any difference in the response of a cell before and during parabrachial activation could not arise as a result of random fluctuations in overall cell responsivity, but must instead represent a consistent and repeatable change in response that is tied to the period of parabrachial activation. Note that the period following each parabrachial activation included sufficient time to ensure a full recovery of the response to control levels, plus an additional pause time of at least 2 s. Intervals between epochs of parabrachial activation thus varied from 4 to 15 s, and care was taken to ensure that this intervening activation interval was well above that required to produce the progressive desynchronization of the EEG, which has been associated with an increase in background activity (Francesconi et al., 1988). The results were evaluated by performing a Fourier analysis within a window one stimulus cycle in length, and this window was swept in 10-ms steps along the length of the response histogram. This provided a continuous record of the change in overall firing rate (F0) and fundamental response magnitude (F1), from which epochs wholly within or beyond the period of parabrachial activation could be selected and averaged.

Results

We examined the effects of parabrachial activation on the spontaneous and/or visually driven activity of 43 cells. Of these, 40 were recorded above lamina A of the lateral geniculate nucleus and had response characteristics that are typical for the perigeniculate nucleus (So & Shapley, 1981; Wrobél & Tarnecki, 1984; Uhlrich et al., 1991). Most had a high level of spontaneous activity and responded to activation of the optic chiasm at latencies in the range expected for perigeniculate neurons. They also responded to a range of drifting sinusoidal gratings both with an overall increase or decrease in firing level and with modulation at the fundamental harmonic frequency. In contrast, the other three cells exhibited no obvious responses either to visual or optic chiasm activation, although their spontaneous activity was clearly inhibited by parabrachial activation. These three were subsequently localized to the region of the thalamic reticular nucleus that overlies the perigeniculate nucleus, and they are not considered further here.

Effect on spontaneous activity

In the absence of visual stimulation, parabrachial activation evoked a clear and consistent suppression of the spontaneous activity in 35 of the 40 cells (88%), examples of which are shown below. In three of these 35 cells, the suppression was preceded by a transient increase in firing rate. Such a phenomenon has been described previously for the thalamic reticular nucleus (Steriade et al., 1986), and we have classified it here as a mixed effect. Thus, a pure suppression was seen for 32/40 (80%) cells. Four cells were unaffected by activation of the parabrachial region at the frequencies and intensities tested, while one cell was excited.

The suppression was seen most clearly with burst activation, which also allowed an estimation of the time course of the effect. This was done for only 25 cells of the 35 showing suppression, since the others had a low rate of bursty discharge that made an accurate assessment of time course impractical. Latency was measured at the onset of the suppression, which was usually very sharp, yielding a mean value of 65 ms (range, 5–395 ms; median, 25 ms). The duration was assessed as the period over which the average activity of the cell was reduced by more than 25% of the control level. The duration had a mean value of 606 ms (range, 50–1600 ms; median, 500 ms). There was considerable variability in these values from cell to cell.

Activation of the parabrachial region with a train of pulses could also produce a profound suppression of spontaneous activity, which lasted throughout the period of activation (see below), although this effect was sometimes weak and difficult to discern. In none of our examples did train activation increase the spontaneous firing rate. Such increases have been described previously by Francesconi et al. (1988), but only with brain-stem activation that was sufficiently intense and prolonged to cause desynchronization of the EEG. In contrast, we took care to ensure that the intensity, duration, and repeat frequency of our parabrachial activation pulses were below the level necessary to produce EEG desynchronization (see Methods), and it is perhaps for this reason that we did not see the effect reported by Francesconi et al. (1988).

Effect on visual activity

The effects of parabrachial activation were profoundly modified by the presence of a visual stimulus. In particular, the degree of suppression evoked by any one parabrachial activation protocol could vary greatly according to the visual stimulus displayed. We were even able to produce a facilitation of the visual response in 30 of our 40 cells (75%) by choosing an appropriate combination of visual and parabrachial stimulus conditions. This group included the cell for which spontaneous activity was also increased by parabrachial activation, the three having a mixed effect, three of those for which spontaneous activity was unaffected, and 23 (72%) of the 32 cells for which spontaneous activity was reduced without any evidence of an initial excitation. Fig. 1 illustrates one such example, showing data for a perigeniculate cell dominated by the contralateral eye. The parabrachial region was activated with a high-frequency burst 900 ms after the start of each 4-s trial period. The effect on spontaneous activity is illustrated in the upper histogram, in which

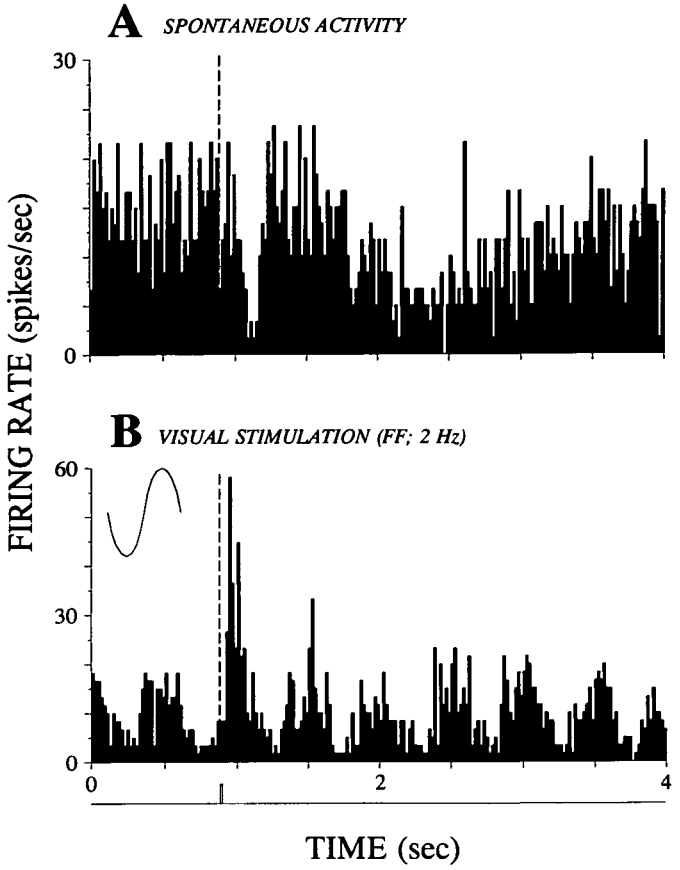

Fig. 1. Effects of burst parabrachial activation on the spontaneous and visually driven activity of a perigeniculate cell. Data were averaged over 30 trials, repeated at 10-s intervals to allow full recovery on each occasion following brain-stem activation. Bin width is 20 ms. The parabrachial region was activated with a high-frequency burst of electrical stimuli (4 pulses at 250 Hz) at the time marked on the trace beneath the lower histogram; this is also indicated by the vertical, dashed line running through the histograms. A: Effects of spontaneous activity showing suppression of responses by parabrachial activation. B: Effects on visually evoked activity. The visual stimulus was a full-field display sinusoidally modulated at 2 Hz, and the sine wave above the left portion of the histogram indicates the phase of the contrast changes in the display. Parabrachial activation produced a transient increase in the visually driven response.

the firing rate was reduced for a period of 120 ms following the parabrachial activation. A slightly weaker but far more prolonged period of suppression occurred at a longer latency. This was seen for a minority of cells and many be a secondary effect rather than a direct consequence of transmitter released from the brain-stem axon terminals. The lower record shows the result of repeating this experiment while the cell was visually driven at a frequency of 2 Hz by a full-field, sinusoidally modulated display. The sine wave above the lower histogram indicates the phase of the contrast change in the visual stimulus. In the control condition before parabrachial activation, the cell clearly responded to the visual stimulus at the fundamental frequency. Parabrachial activation increased both the depth of modulation and the overall activity of the cell. A comparison of the two response histograms indicates that the period of enhanced response to the visual stimulus (lower histogram) slightly preceded the phase of maximal inhibition seen during spontaneous activity (upper histogram).

Fig. 2 shows the effect of activation of the parabrachial region on spontaneous and visually driven activity for two perigeniculate cells. These cells illustrate the two extremes observed for the range of effects caused by parabrachial activation. The data are plotted both as response histograms and also in terms of the average discharge (F0) and fundamental response amplitude (F1) of the activity at different points throughout each trial (see Materials and methods). For the cell illustrated in Figs. 2A–2C, burst activation of the parabrachial region elicited a transient suppression of the spontaneous firing rate (Fig. 2A). This cell thus appeared to receive a purely inhibitory input from the parabrachial region. During visual stimulation, the cell gave a well modulated, strongly rectified response at the fundamental frequency of the stimulus. This response increased dramatically throughout a 500-ms period of low-frequency, train activation of the parabrachial region (Fig. 2B). As shown in Fig. 2C, the F1 and F0 response components increased in parallel. The effect on the cell shown in Figs. 2D–2F was more complex. In this case, train activation of the parabrachial region was used both during spontaneous and visually driven activity. The parabrachial activation powerfully suppressed the spontaneous activity of this cell, and thus the parabrachial input again seemed to be strongly inhibitory in the absence of a visual stimulus. During visual stimulation and before parabrachial activation, the cell responded with a small-amplitude modulation at twice the stimulus frequency (not shown in the bottom graph of Fourier components). Parabrachial activation reduced the average firing rate, which is reflected by the fall in the F0 component of the Fourier analysis. At the same time, however, the cell began to respond very well at the fundamental harmonic frequency. Hence, the F1 component of the response increased despite the reduction in the F0 response component. This indicates a marked increase in the visual signal transmitted through the perigeniculate cell, which can be described quantitatively in terms of an increase in the F1/F0 ratio (see below).

Effect on spatial and temporal frequency tuning

As noted above, 30 of the 40 perigeniculate cells tested exhibited enhanced visually evoked responses during parabrachial activation for at least some combination of electrical and visual stimuli. However, the effects of parabrachial activation clearly depended on the spatiotemporal parameters of the visual stimulus. We examined spatial and/or temporal tuning for a subset of 20 of our sample of 40 perigeniculate cells.

Fig. 3 illustrates for one perigeniculate cell the effect of parabrachial train activation on the spatial tuning, tested at a temporal frequency of 2 Hz. The tuning curves on the right plot the magnitude of the fundamental harmonic response against the spatial frequency of the visual stimulus, recorded before and during the period of parabrachial activation. Three of the data points, one showing suppression of the response, one no effect, and the other a marked facilitation, are also represented by response histograms on the left. Before parabrachial activation, the cell responded best to the lower spatial frequencies and thus exhibited low-pass spatial characteristics. Activation of the parabrachial region, however, suppressed the responses below 0.25 cycles/deg while facilitating those to the higher spatial frequencies, so that the optimal response shifted dramatically towards higher spatial frequencies. The cell also became more sharply

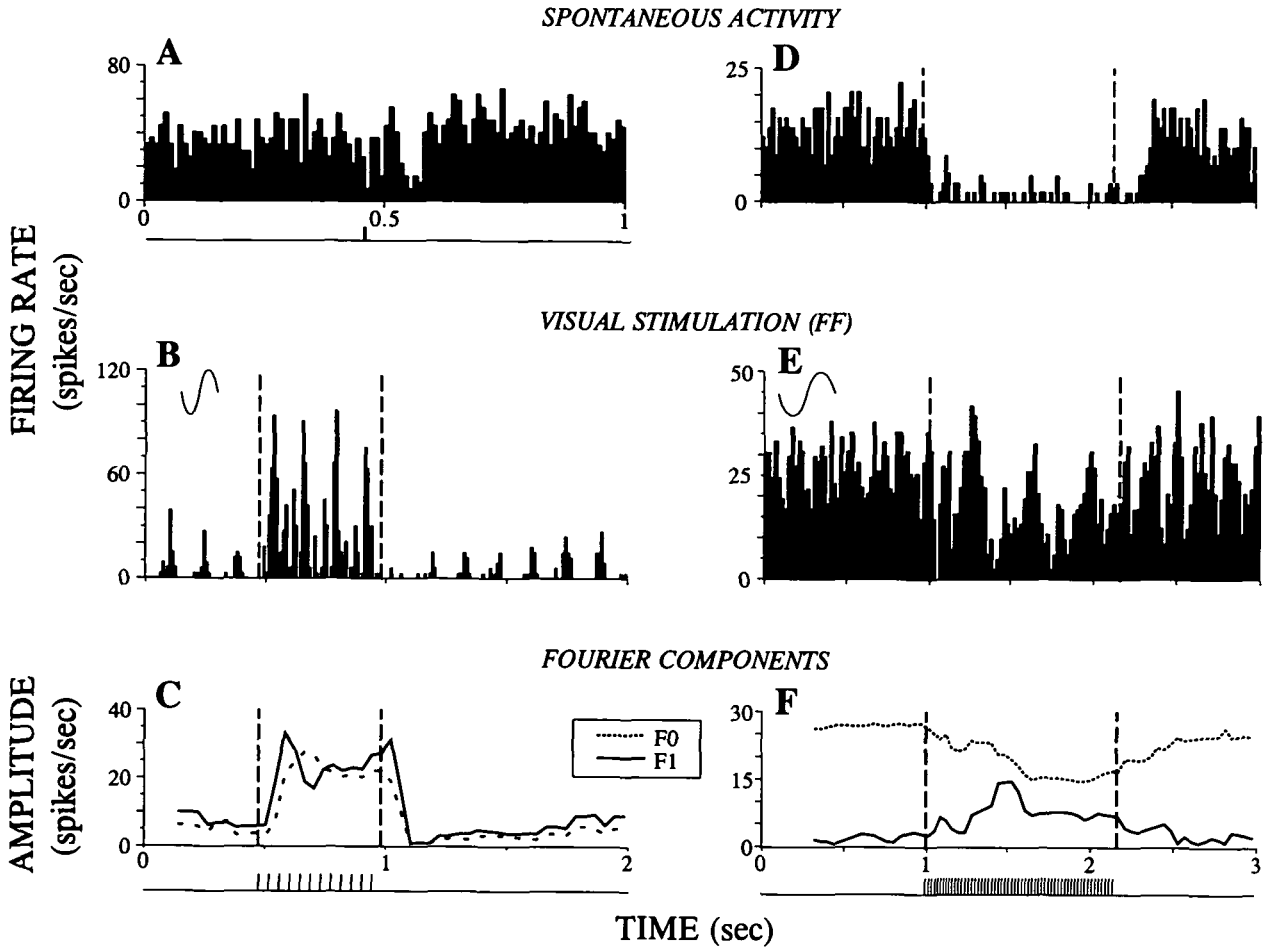

Fig. 2. Effects of parabrachial activation on the spontaneous and visually driven activity of two perigeniculate cells. A: Effects on spontaneous activity of the first cell, showing suppression of responses by parabrachial burst activation applied at the time indicated on the trace below the histogram. B: Effects on visually evoked activity of the cell in A. Parabrachial activation in this case consisted of a train of shocks (25 Hz for 500 ms) as indicated by the marks on the trace below C and the vertical, dashed lines. The visual stimulus was a full-field display sinusoidally modulated at 7.25 Hz. C: Fourier analysis of the visual response in B, showing the magnitude of the average discharge rate (F0) and the fundamental frequency component (F1) at different points in the test cycle. Note the prominent enhancement of the visually evoked response during parabrachial activation, which increased both F1 and F0 response elements in parallel. Bin width for A and B is 10 ms; data were averaged over 33 trials, repeated at 4-s intervals. D: Effects on spontaneous activity of the second cell, showing suppression of responses by parabrachial train activation (50 Hz for 1 s) applied at the time bounded by the vertical, dashed lines and indicated on the trace below the histogram in F. E: Effects on visually evoked activity of the cell in D, with the same train activation. The visual stimulus was a full-field display sinusoidally modulated at 3 Hz. F: Fourier analysis of the visual response in E; conventions are as in C. Note the enhancement of the F1 response component despite suppression of the overall response (F0). Bin width for D and E is 20 ms; data were averaged over 41 trials and repeated at 5-s intervals. Other conventions are as for Fig. 1.

tuned. Fig. 4 illustrates the effect of parabrachial activation on the temporal tuning of the same cell, tested with a sinusoidally modulated full-field display. As can be seen, parabrachial activation suppressed the response to the full-field stimulus at 2 Hz, which is consistent with the effect shown in the previous figure for the same visual stimulus combination. Note that this was the case despite a doubling of the rate of parabrachial activation. However, responses were facilitated at higher temporal frequencies.

The influence of parabrachial activation on spatial tuning was tested for 17 cells at one or more temporal frequencies, and the influence on temporal tuning was tested for 14 cells at one or more spatial frequencies; both spatial and temporal frequency tuning curves were constructed for 11 of these cells. The tuning curves obtained during the control condition differed radically from cell to cell, which is consistent with the known response characteristics of the perigeniculate nucleus (So & Shapley, 1981; Wrobél & Tarnecki, 1984). The combination of facilitation at some frequencies and suppression at others altered the shape of the tuning curves for many cells. Where the experiment was repeated for a given cell the pattern of effect was replicated, but it differed from one cell to the next. In all, 3/17 spatial and 3/14 temporal tuning curves changed beyond all recognition, while five spatial and three temporal tuning curves showed a shift in tuning width and/or optimal frequency while retaining a similar basic shape. The remainder showed only random or minor variations from their original characteristics. It should be noted that changing either the frequency or duration of the

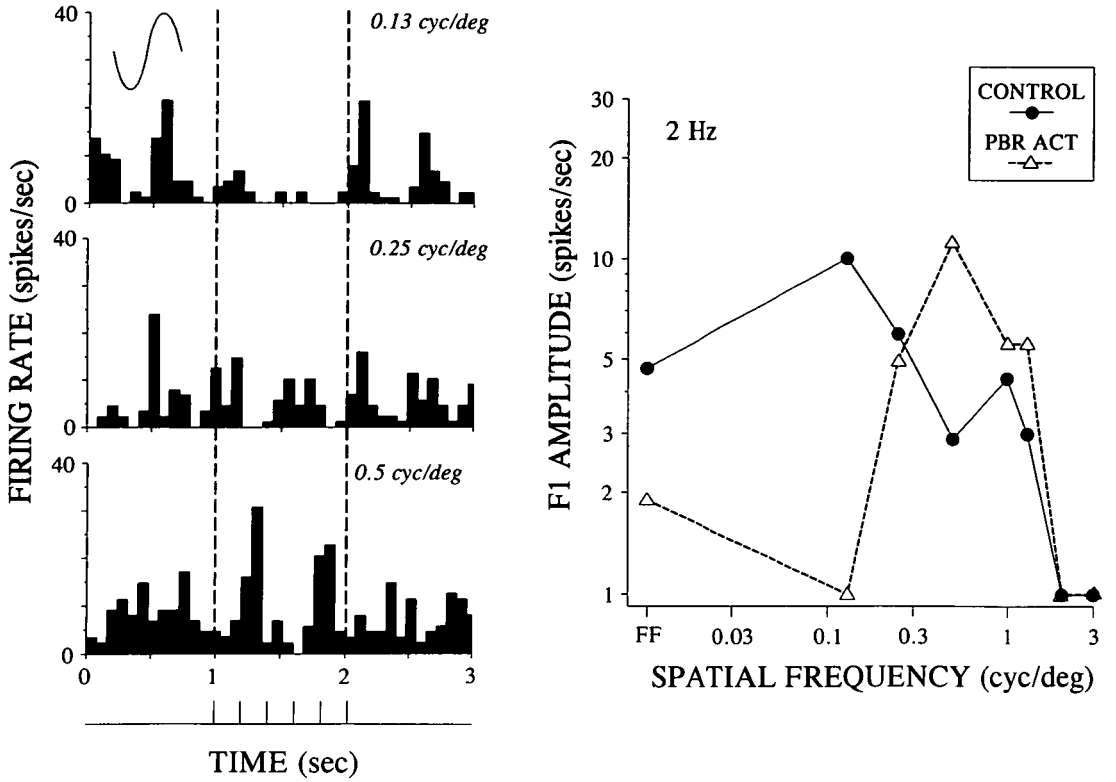

Fig. 3. Effects of parabrachial train activation on responses of a perigeniculate cell to gratings at a range of spatial frequencies drifted at 2 Hz or to a full-field display modulated at the same frequency. The spatial tuning curves on the right represent the F1 amplitude at each frequency, before and during parabrachial activation (5 Hz for 1 s), while histograms on the left illustrate responses at three of the spatial frequencies, using conventions as for Figs. 1 and 2. Data were averaged over 11 trials; bin width is 80 ms. Note that parabrachial activation shifted the optimal response toward higher frequencies.

parabrachial activation could alter the degree of facilitation or inhibition, such that the tuning curve obtained during parabrachial activation was shifted up or down. Thus, a visual response that was facilitated under one set of electrical stimulus conditions might be reduced under another, but the shape of the tuning curve obtained during parabrachial activation remained the same in either case.

We found no consistent correlation between either the spatial or the temporal frequency of the visual stimulus and the observed changes for any of the response measures used (F0,

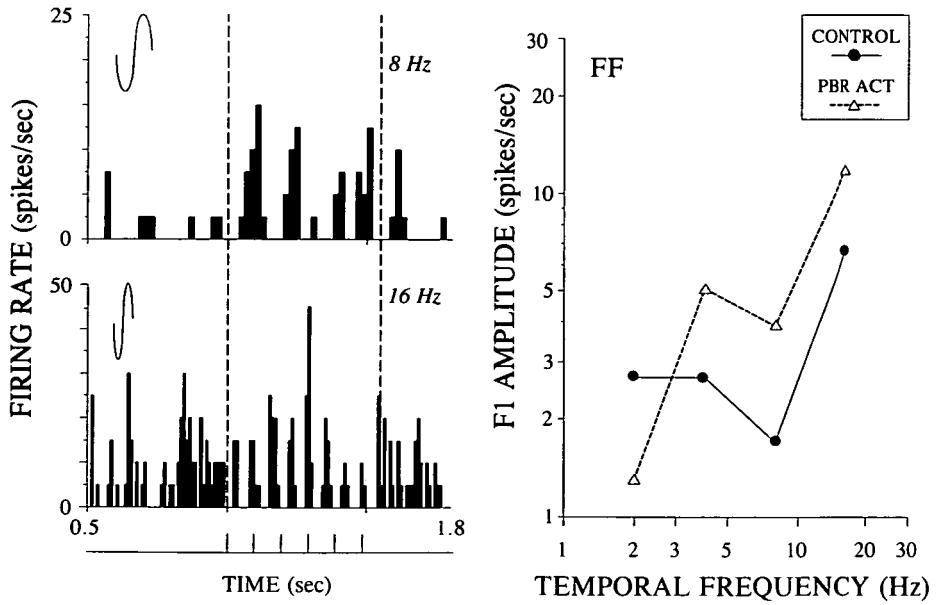

Fig. 4. Effects of parabrachial train activation on responses of the same perigeniculate cell as in Fig. 4 to a range of temporal frequencies; conventions are as in Fig. 4, except that temporal rather than spatial tuning is shown, and a higher frequency of parabrachial activation was used (10 Hz for 0.5 s). Visual stimuli consisted of a full field display modulated at the temporal frequencies indicated. Data were averaged over 20 trials; bin widths are 20 ms (top) and 10 ms (bottom). Note that the response to the 2-Hz stimulus was again suppressed as in Fig. 4.

F1, or the F1/F0 ratio) following parabrachial activation. Therefore, the examples shown in Fig. 5 for spatial tuning and Fig. 6 for temporal tuning simply illustrate a few of the more notable patterns of effect. Fig. 5A represents a cell for which parabrachial activation reduced the visually evoked response over a wide range of spatial frequencies, this being one example where no evidence of a facilitation was seen for any combination of stimuli tested. This example is also unusual in that there was little change in the shape of the tuning curve. The example in Fig. 5B was inhibited most strongly at the higher and lower spatial frequencies with little change in the responses to intermediate stimuli. The overall result was a more sharply tuned cell with band-pass characteristics. Fig. 5C shows a cell exhibiting increased responses to full-field stimuli with parabrachial activation but little effect in response to other spatial patterns. Finally, Fig. 5D represents a cell for which parabrachial activation induced a large shift in optimal response towards the higher spatial frequencies. Fig. 6 illustrates two different effects of parabrachial activation on temporal tuning. In the example of Fig. 6A, parabrachial activation suppressed the response to high and low temporal frequencies, which rendered a cell that was broadly tuned for temporal frequency to one that displayed band-pass tuning. Fig. 6B shows an example of the opposite effect. Again, these cells represent the extreme ends of a wide spectrum of observed effects of parabrachial activation on the temporal tuning of perigeniculate cells.

The responses of perigeniculate cells are notoriously variable, and we observed changes in the control response characteristics of some cells that were retested over prolonged periods of time. This was presumably a consequence of small drifts in the state of the preparation, which would in turn involve a shift in the level of activity in the modulatory pathways, including the input from the parabrachial activation. Our control and activation data were interleaved and paired on a trial-by-trial basis, so such variation in overall state of the preparation was unlikely to affect our data. Nonetheless, in order to control for this further, we ran the following experiment on a number of cells. The intensity of the parabrachial activation was turned down to below the threshold level for an effect, and a spatial or temporal tuning curve was constructed using our normal criteria. Under these circumstances, the tuning curves constructed for the control and subthreshold activation conditions did not differ. This confirms that the changes we did see were a consequence of effective parabrachial activation.

Although Figs. 1 and 2 provide examples of parabrachial activation enhancing visually evoked responses in the same cells for which it suppresses spontaneous activity, Figs. 3–6 show that these facilitatory effects cannot be generalized over a wide range of spatial and temporal frequencies of visual stimulation. Indeed, for all but one perigeniculate cell, the responses to the majority of visual stimulus conditions, represented by different spatial and temporal frequencies, were actually suppressed. The range of effects seen over the entire series of experiments is summarized in Fig. 7, which shows the change in visual response for the various stimulus conditions. Note that only the 35 perigeniculate cells for which spontaneous activity was inhibited by parabrachial activation were used in this analysis, and that only data involving train activation of the parabrachial region were considered appropriate for the Fourier analysis of the modulated F1 visual response component. Fig. 7 includes all of the 152 experimental conditions (i.e. various spatiotemporal stimulus variables) tested with these criteria. Fig. 7A

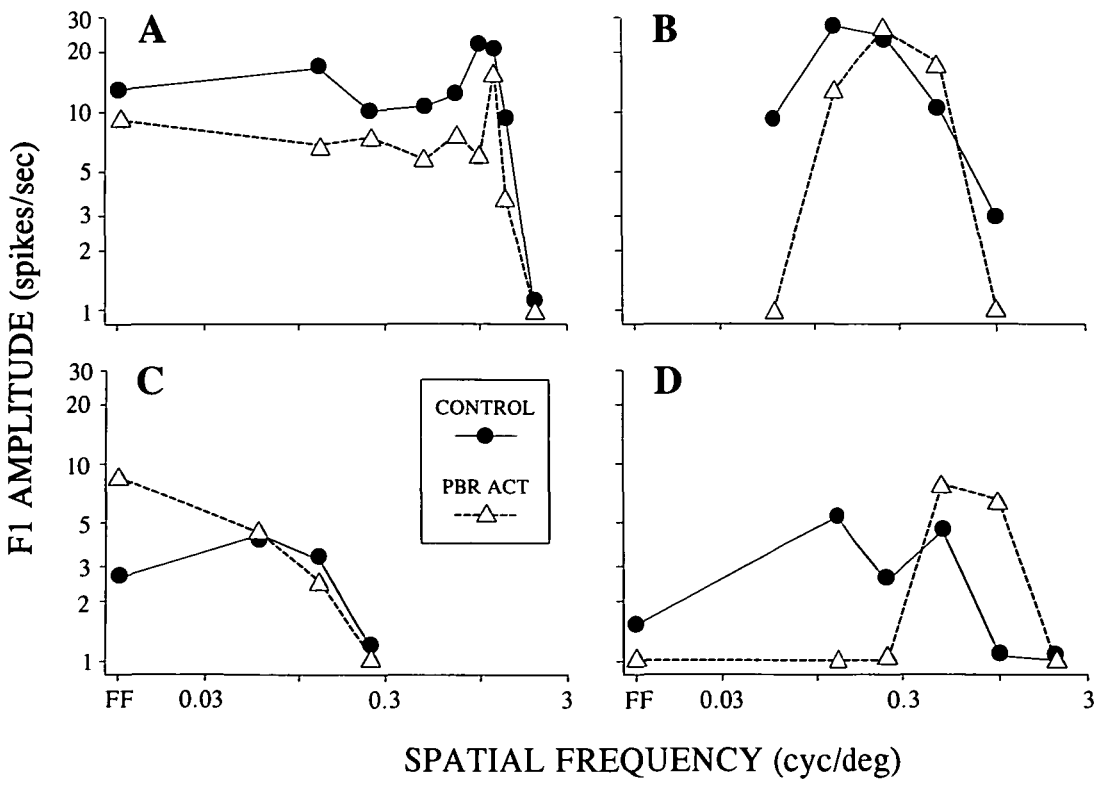

Fig. 5. Examples illustrating effects of parabrachial train activation on spatial tuning for four perigeniculate cells.

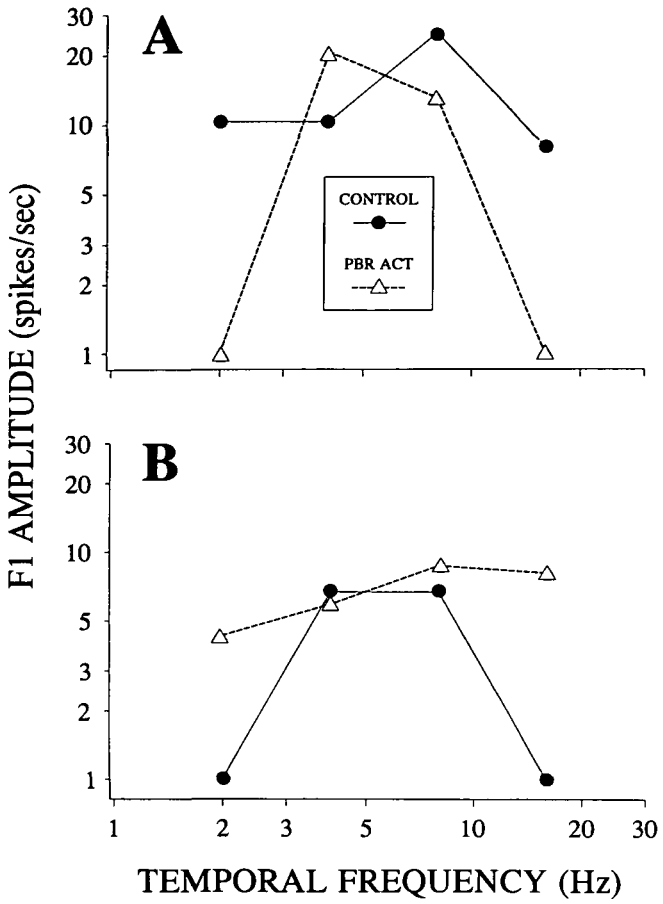

Fig. 6. Examples illustrating effects of parabrachial train activation on temporal tuning for two perigeniculate cells.

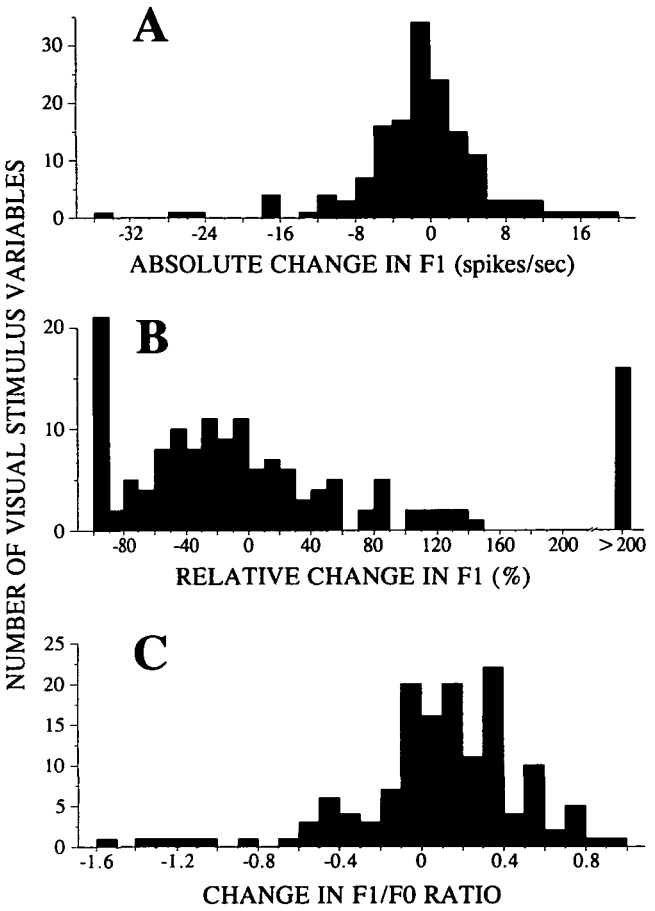

Fig. 7. Histograms showing the range of effects of parabrachial activation on responses evoked by each of the visual stimuli employed for all perigeniculate cells showing parabrachial suppression of spontaneous activity (see text for details). A: Absolute change in the fundamental Fourier response component. B: Relative change in the fundamental Fourier response component. C: Change in the ratio between the fundamental Fourier response component and the overall response.

expresses the change as an absolute increase or decrease in the modulated (F1) response rate, while Fig. 7B replots the same data in terms of a change in the modulated (F1) response relative to the control response level in the period preceding parabrachial activation. Overall, the visually evoked response was suppressed for 86 conditions (57%), enhanced for 63 (41%), and remained unchanged for 3 (2%). Changes in these responses induced by parabrachial activation exceeded 10% of control values in 135 conditions (89%) and exceeded 20% of control values in 119 conditions (78%). Finally, Fig. 7C shows the change in the ratio of the modulated (F1) response to the overall response (F0) brought about by parabrachial activation. The F1/F0 ratio is analogous to the signal-to-noise ratio, because the modulated discharge (F1) carries the signal, while the overall activity (F0) is a measure of background activity against which the signal must be detected. Although there is considerable scatter, parabrachial activation on average evokes a significant increase in the F1/F0 ratio ($P < 0.02$ on a paired t-test).

Discussion

The data reported here show that activation of inputs from the largely cholinergic parabrachial region of the brain stem to the thalamus does not have an exclusively inhibitory effect on cells in the perigeniculate nucleus, as has previously been assumed. In particular, we have shown that this input has the potential to exert a differential effect on the spontaneous and visually driven discharges of many perigeniculate cells. Background activity was strongly inhibited for almost every cell tested, with a latency and duration that are within the range reported previously for both the perigeniculate nucleus specifically and the thalamic reticular nucleus more generally (Singer, 1973; Dingledine & Kelly, 1977; Francesconi et al., 1988). In contrast, parabrachial activation could exert a range of effects on the visually driven activity of those same cells, depending on the visual stimulus parameters tested. That is, such activation could suppress the responses to some visual stimuli, while facilitating the responses to others. This results in a substantial modification of the spatial and temporal tuning properties of many perigeniculate cells. This effect has not been reported previously, and it has important consequences for the way in which we view the role of the perigeniculate nucleus in gating retinogeniculate transmission.

Attempts to define the role of the perigeniculate nucleus in visual processing have given rise to an apparent paradox. On the one hand, in the anesthetized animal the receptive fields of perigeniculate cells are poorly localized and unselective com-

pared with those of the lateral geniculate nucleus, and their responses are erratic and highly variable (So & Shapley, 1981; Wrobél & Tarnecki, 1984). They thus appear to be poor mediators for visually specific inhibition. Instead, this suggests that perigeniculate cells might globally gate retinogeniculate transmission depending on the overall state of the animal. Arousal is associated with an increase in the activity of a number of modulatory inputs to the thalamus (Trulson & Jacobs, 1979; Aston-Jones & Bloom, 1981), some of which are facilitatory to perigeniculate cells (McCormick, 1989; McCormick & Wang, 1991). These inputs could potentially support an improvement in the level of visual responsiveness on arousal. However, they seem to be opposed by the massive cholinergic projection from the parabrachial region (Steriade et al., 1982). Since the spontaneous activity of perigeniculate cells is inhibited both by the iontophoretic application of acetylcholine (Phillis et al., 1967; Godfraind, 1978; Sillito et al., 1983) and by activation of the input from the parabrachial region (Singer, 1973; Fukuda & Stone, 1976; Dingledine & Kelly, 1977; Ahlsén et al., 1984; Francesconi et al., 1988), it has been assumed that this pathway must have a globally suppressive effect on perigeniculate activity in the awake and attentive animal, in turn globally disinhibiting geniculate relay cells and thus globally enhancing retinogeniculate transmission. On the other hand, the perigeniculate nucleus sits in the pathway between the lateral geniculate nucleus and the visual cortex, receiving collateral inputs both from the geniculate relay cells that project to the cortex, and from the cortical cells that feed back to the lateral geniculate nucleus (Dubin & Cleland, 1977; Friedlander et al., 1981; Ahlsén & Lindström, 1982; Ide, 1982). Both inputs are retinotopically organized (Sanderson, 1971; Updyke, 1975; Friedlander et al., 1981), as is the output from the perigeniculate nucleus to the lateral geniculate nucleus (Uhlrich et al., 1991), giving a level of retinotopic order that suggests more than a global or general gating function.

Our data provide a solution to this problem, by showing that parabrachial input has the potential to enhance the visual signal conveyed by perigeniculate cells, by either increasing or simply sparing their responses to a limited range of visual stimuli, and thus sculpting their visual response profiles. One important caveat is that although the observed facilitations were in some cases robust, in others they could be evoked only over a limited range of electrical activation frequencies. It is thus difficult to extrapolate these results to changes in parabrachial activity in the awake, behaving animal. Nevertheless, this observation is consistent with two changes associated with arousal from slow wave sleep: an increase in perigeniculate cell activity (Mukhametov et al., 1970), and improved visual selectivity of geniculate cells (Livingstone & Hubel, 1981). It also supports our own data showing that parabrachial activation can enhance the effectiveness of the inhibitory surround for a proportion of geniculate cells (Uhlrich et al., 1989).

The mechanisms underlying the facilitation are open to question. One consideration is that other, noncholinergic neurotransmitters or neuromodulators may be involved. Some cholinergic cells in the parabrachial region colocalize neuroactive peptides (Vincent et al., 1986), and most that project to the later geniculate nucleus colocalize NADPH-diaphorase, which is associated with the synthesis of nitrous oxide (Bickford et al., 1993*a*). The effects of these neurotransmitters are not known, but either could mediate the transient excitation in thalamic reticular cells seen following rostral brain-stem activation (Steriade et al., 1986) and reported here for a small minority of perigeniculate cells. Similarly, although our stimulating electrodes were optimally located to activate cholinergic parabrachial cells (DeLima & Singer, 1987; Uhlrich et al., 1988), there is no guarantee that axons of passage from other brain-stem regions were not also affected. Both norepinephrine (McCormick, 1989) and serotonin (McCormick, 1989; McCormick & Wang, 1991) can depolarize thalamic reticular and perigeniculate cells. However, the important point here is that the cells selected for detailed analysis in this study were all inhibited by parabrachial activation in the absence of a visual stimulus, with no sign of an excitatory or facilitatory response. Therefore, explanations involving the action of neuroactive substances other than acetylcholine are incomplete. Nevertheless, this question will need to be addressed in future experiments.

Another possibility is that acetylcholine itself is responsible for both aspects of the dual response to parabrachial activation. It has been suggested that cholinergic hyperpolarization could directly increase the visual responses of perigeniculate cells, by activating the low-threshold calcium conductance and so increasing their tendency to respond to depolarizing stimuli with a burst of high-frequency discharges (McCormick & Prince, 1986). The responses to grating stimuli, which provoke alternating waves of depolarization and hyperpolarization, are especially likely to be sensitive to this kind of influence, particularly at certain temporal frequencies.

In our view, however, the most straightforward explanation derives from observations that activation of the parabrachial region greatly increases the visual responsiveness of geniculate relay cells (Singer, 1973; Francesconi et al., 1988), and this seems likely due to a cholinergic excitation (Sillito et al., 1983; Francesconi et al., 1988) following depolarization involving nicotinic and muscarinic receptors (McCormick & Prince, 1987). Furthermore, increased responsiveness of geniculate relay cells most likely leads to increased responsiveness of visual cortex and thus corticogeniculate axons, which are known to be facilitated by brain-stem activation (Singer et al., 1976). The overall effect will be to greatly increase the magnitude of the afferent drive from the lateral geniculate nucleus and visual cortex to the perigeniculate nucleus, and this alone may be sufficient under certain conditions to counter the cholinergic inhibition. For two reasons, those conditions are most likely to be met during visual stimulation than during epochs of spontaneous activity. Since visual stimulation generally evokes higher peak activity levels in geniculate and cortical cells than seen during spontaneous activity, extra excitatory drive is available to perigeniculate cells to overcome the cholinergic inhibition. Furthermore, visual stimuli will serve to synchronize activity among inputs to perigeniculate cells from neighboring geniculate and cortical cells, thereby evoking a more strongly modulated postsynaptic response. The effect of parabrachial activation on perigeniculate cells could therefore be determined by the balance between direct inhibitory and indirect excitatory influences, and it follows that the stimulus dependence of the effect would in turn depend upon the visual response properties of the afferent cells and their relative sensitivity to parabrachial activation.

Whatever the specific mechanism, it now seems possible that the function of this pathway from the parabrachial region may be to suppress the responses of perigeniculate cells to weaker inputs, as well as to nonspecific and spontaneous activity, while allowing more powerful visually driven excitatory inputs to function. This would have the advantage of increasing the localization and selectivity of their otherwise large and poorly selective

receptive fields, while under some circumstances improving the magnitude and signal-to-noise ratio of the remaining responses. Combined with the more obviously facilitatory influence of the noradrenergic and serotonergic pathways, it offers a mechanism with the potential to convert the poor visual responses typical of perigeniculate cells in the anesthetized preparation into an effective source of the visually selective inhibition.

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