Brainstem control of response modes in neurons of the cat's lateral geniculate nucleus

(X cells/parabrachial region/retinogeniculate transmission/receptive fields)

D. J. UHLRICH, N. TAMAMAKI, AND S. MURRAY SHERMAN

Department of Neurobiology, State University of New York, Stony Brook, NY 11794-5230

Communicated by James M. Sprague, January 19, 1990 (received for review November 8, 1989)

ABSTRACT The visual pathway from retina through the lateral geniculate nucleus to visual cortex in the cat is comprised of several parallel neuronal streams that independently analyze different aspects of the visual scene. The best known of these are the X and Y pathways that relay through the geniculate A laminae. Recent receptive-field studies of retinal and geniculate neurons suggest that there is a further elaboration of cell types at the level of the lateral geniculate nucleus. That is, two types of geniculate X cells with different temporal patterns of responses to visual stimuli are recognized, one with "nonlagged" features, exhibiting shorter response latencies and another with "lagged" features; all retinal X cells are nonlagged. We asked whether nonlagged and lagged responses represent different cell classes or two response modes of the same cells, perhaps under the control of nonretinal afferents to these relay cells. Accordingly, we studied the effects on appropriate receptive-field properties of electrical activation of the midbrain parabrachial region, which is a major nonretinal input to relay cells. Such parabrachial stimulation made each of the eight lagged X cells much more like nonlagged cells, and this stimulation completely transformed the lagged response profiles of six of the eight cells to nonlagged. We thus conclude that the property of lagged responsiveness, which is an emergent property of the lateral geniculate nucleus, is a different response mode of the same cells that can also display nonlagged responses, rather than representing different cell classes; furthermore, this switching between response modes is, at least partly, under the control of afferents from the parabrachial region.

In general, sensory signals are not simply relayed to cortex via the thalamus: the thalamus acts instead as a variable gateway for this relay (1, 2). When the gate is wide open, the signals are simply relayed; when closed, nothing gets through; when partly opened, some signals get through, depending on which filters are set. The lateral geniculate nucleus provides an excellent example of this gating for visual signals (1, 3, 4). Nonretinal afferents to geniculate relay cells, which represent 80–90% of the synaptic input to these cells (5, 6), play a crucial role in setting the gain of retinogeniculate transmission, making the lateral geniculate nucleus a variable gateway for retinal signals to cortex (1, 3, 4). These nonretinal inputs derive from local, γ -aminobutyric acid-releasing (GABAergic and thus probably inhibitory) neurons, from the visual cortex, and from various brainstem sites (1–4). Probably chief among the brainstem afferents are cholinergic axons emanating from the parabrachial region (1, 2).

A question still to be addressed is precisely what transformations of retinogeniculate transmission are controlled by these nonretinal afferents. Perhaps the most dramatic recent example of such a transformation stems from evidence that

the two main parallel pathways, X and Y (7–9), that innervate the lateral geniculate nucleus from retina are transformed into at least three pathways to cortex. This is because one of them, the X pathway, seems to divide into "nonlagged" and "lagged" classes (10–13). All afferent retinal X axons are of the nonlagged type, which implies that lagged X cells are an emergent property of geniculate circuitry (10, 11). However, rather than representing two distinct neuronal classes, it is possible that nonlagged and lagged X cells are two response modes of the same neurons and that a nonretinal input to the lateral geniculate nucleus, such as the parabrachial region of the midbrain (1–4), controls which response mode is expressed. This is, indeed, what we conclude, because we found that the responses of most lagged X cells could be converted to nonlagged X cells by appropriate activation of this parabrachial region.

MATERIALS AND METHODS

We used conventional techniques (14, 15) to record extracellularly from cells of the geniculate A laminae in cats that were anesthetized with halothane and paralyzed. The recording electrodes were fine-tipped micropipettes (filled with 0.2 or 3 M KCl and beveled to a final impedance of 10–60 M Ω at 100 Hz). We inserted one pair of bipolar stimulating electrodes to straddle the optic chiasm and introduced another into the midbrain parabrachial region (cf. ref. 16). We applied single pulses (50- to 100- μ sec duration, 150–700 μ A) across the chiasm electrodes to activate geniculate cells orthodromically, and we stimulated the parabrachial region with similar pulses in trains (50 Hz and 500- to 1000-msec duration) to activate its ascending input to the lateral geniculate nucleus (for reviews of the latter, see refs. 1–4). After plotting receptive fields on a frontal tangent screen, we placed in front of the cat a cathode ray tube on which two types of visual stimuli were generated under computer control, and we also used the computer to analyze the neuronal responses. One type of stimulus was a series of counterphase-modulated sinusoidal gratings with maximum contrast of 0.6, space average luminance of 40 cd/m², modulation rate of 2 Hz, and spatial frequency that could be continuously varied. The other stimulus consisted of a spot roughly the diameter of and centered on the receptive field center. It flashed on and off the 40 cd/m² background at various fixed frequencies (usually 1–3 Hz). For On-center cells, the spot luminance was 64 cd/m² and for Off-center cells, it was 16 cd/m².

We first identified the neuronal class of the cells recorded in the A laminae as X or Y and On or Off center. The X/Y identification was based on a battery of tests, including linearity of summation in response to the grating stimuli, receptive-field center size, and response latency to optic chiasm stimulation (7–9). The remainder of this report is concerned only with X cells. We subdivided the X cells into lagged and nonlagged types. To do this, we strictly adhered to previously published criteria. That is, we measured the latency needed for the cell to reach half its peak firing rate in

response to the spot stimuli described above; this latency for every lagged cell is >70 msec, whereas for 90% of nonlagged X cells, it is <60 msec (10, 12). Also, the lagged X cells displayed a more sustained response than did nonlagged X cells to the spot stimuli, and lagged X cells often produced an anomalous "off" response (i.e., the discharge of an On-center cell to turning the spot off or of an Off-center cell to turning the spot on), something not seen in nonlagged X cells (10, 12).

RESULTS

We studied 41 X cells with receptive fields within 20° of the area centralis. Based on the criteria described in *Materials and Methods*, 8 of these 41 X cells were lagged (6 On-center and 2 Off-center cells), and the remainder were nonlagged (16 On-center and 17 Off-center cells). We found X cells with lagged responses to be somewhat rarer than the one-third to one-half of X cells reported (10, 12). It is unclear whether this result is due to electrode sampling or some subtle difference among physiological preparations that might affect the lagged-response property.

Our major observation is that the majority of lagged X cells (six of eight) could readily be converted to nonlagged X cells by appropriate activation of the parabrachial region of the midbrain. By "appropriate," we mean trains of electrical shocks long enough to span at least one visual stimulus cycle.

Parabrachial activation also rendered the other two lagged cells less lagged, but not sufficiently to make them nonlagged (see also below). For nonlagged cells, such appropriate parabrachial activation did not qualitatively change the response profile to spot stimuli, although it generally enhanced the response of the cells.

Fig. 1 illustrates this phenomenon for four representative X cells, two nonlagged and two lagged. Note that the two nonlagged X cells responded briskly to onset of the spot and that the stimulus cycles coinciding with parabrachial activation evoked somewhat stronger responses (Fig. 1 A and B). Nonetheless, the response profile remained fairly constant throughout, and the latencies to half the response peak remained <70 msec with little variation. These latencies are well within the range expected for nonlagged X cells. However, spot onset evoked a slowly building response in the lagged X cells until the parabrachial region was activated (Fig. 1 C and D). Before parabrachial activation, the latencies to half the response peak were >100 msec, indicative of lagged responses, but during such activation (and often after it for variable periods), these latencies fell to <60 msec, indicative of nonlagged responses.

Fig. 2 A–E shows this phenomenon in more detail for the same cells as in Fig. 1 plus an additional lagged X cell. Each of these histograms represents the average response to several cycles of the spot stimulus, and the responses before and

FIG. 1. Peristimulus time histograms showing the responses of two nonlagged (A and B) and two lagged (C and D) X cells to a square-wave-modulated, flashing spot stimulus. The time courses of visual and brainstem stimulation are indicated below each histogram. Each of these is an On-center cell, and thus spot onset involves an increase of light in the center (see text). Half-peak latencies for each excitatory response were extrapolated and are indicated in msec above each stimulus cycle. The asterisks above the last cycle in C denote an unclear response. Note that parabrachial stimulation has virtually no effect on the latencies of nonlagged X cells, but latencies for lagged X cells are dramatically reduced.

FIG. 2. (A–E) Comparison of responses to visual stimulation for nonlagged (A and B) and lagged (C–E) X cells. Two conditions are shown: before parabrachial stimulation (spot alone) and during parabrachial stimulation [parabrachial region (PBR) + spot]. These histograms show responses similar to those illustrated in Fig. 1, except the time base has been expanded, several cycles are averaged for each condition, and histograms for the two conditions are superimposed for easier comparison. The cells in A–D are On-center, so spot on means an increase of light in the center; the cell in E is Off-center, so spot on means a decrease of light in the center. (F) Response latencies to visual stimulation for each of the 33 nonlagged and 8 lagged X cells. The latencies refer to the time needed after spot onset to achieve half the peak firing rate (10, 12). For each cell, the latency to spot onset alone is plotted on the abscissa (Control latency), and the latency to spot onset during parabrachial activation is plotted on the ordinate (PBR latency). Also shown is a line with a slope of 1 (---) and the 70-msec latency below which only nonlagged cells reside (..... perpendicular to each axis). Note that latencies for all nonlagged cells fall very close to the line of slope 1, whereas those of lagged cells are shifted to lower latencies by parabrachial activation.

during parabrachial stimulation are superimposed for easier comparison. Again, the effects of parabrachial activation on nonlagged X cells seemed limited to an enhancement of the response to the flashing spot (Fig. 2 A and B). However, for the lagged X cells, parabrachial activation caused the spot to evoke an early, brisk response that was missing without this activation (Fig. 2 C–E). Note also that the anomalous “off” response seen clearly without parabrachial activation in the lagged X cell of Fig. 2E is effectively masked by the enhanced response to spot onset seen with parabrachial activation.

Two lines of evidence argue against the possibility that the early response peak exposed by parabrachial stimulation in lagged X cells is simply a response to this activation alone. (i) Although parabrachial activation by itself caused an elevation in the firing rate of geniculate neurons (data not shown), rarely was such a clear, distinct peak seen. (ii) More importantly, the early responses exposed in this way were phase-locked to the spot stimulus, not to the parabrachial activation, so that variations in the interval between parabrachial and spot stimulation never altered the phase relationship between the response and spot.

Fig. 2F summarizes the effects of parabrachial activation on the latencies to half the response peak measured for our cell sample. These latencies are shown for each cell before and during parabrachial activation. The lines perpendicular to each axis (dotted lines) indicate the 70-msec latency below which all X cells are nonlagged (10, 12). Note that, for the nonlagged X cells, parabrachial activation had virtually no effect on these latencies because they all fell close to the line of slope 1. Indeed, for the nonlagged cells, these latencies

were 47 ± 13 msec (mean $\pm$ SD) in both conditions. However, for each of the eight lagged X cells, parabrachial activation dramatically reduced these latencies from 151 ± 41 msec to 65 ± 27 msec, a latency reduction of 86 ± 26 msec. The differential effect between nonlagged and lagged cells is statistically significant ($P < 0.001$ on a Mann–Whitney *U* test). Even more interesting, the significant latency difference between the nonlagged and lagged cells without parabrachial activation ($P < 0.001$ on a Mann–Whitney *U* test) becomes nonsignificant with such activation, even with the two cells that cannot be completely converted to nonlagged ($P > 0.1$ on a Mann–Whitney *U* test).

This latency reduction moved six of the lagged X cells from clearly within the lagged range to well within the nonlagged range. The two lagged X cells that parabrachial activation failed to switch completely to nonlagged were the only two lagged cells recorded from a single cat, and they also had the longest latencies of any cells. It is possible that this represents some uncontrolled variable particular to that preparation, such as poor parabrachial electrodes, etc.; it may also reflect the possibility that some cells can be more lagged than others, rendering them more difficult to convert to nonlagged. This question requires further study.

DISCUSSION

We have thus confirmed earlier reports (10–13) that, in the anesthetized, paralyzed cat, the responses of geniculate X cells to visual stimuli can be identified as lagged or nonlagged. However, our data, at the very least, raise questions about whether these response types are isomorphic with cell types.

It now seems quite plausible that the lagged and nonlagged categories represent two different response modes of the *same* cells. It is worth noting that, regardless of whether lagged and normal responses connote different cell types or different response modes of the same cells, this still represents an emergent property of the lateral geniculate nucleus.

While this notion of cell classification should be pursued, our data do not yet make clear how many classes of geniculate X cell exist. On the one hand, it may be that only a subset of X cells can enter the lagged response mode, so that even though all X cells may be able to respond in a nonlagged fashion with an active midbrain parabrachial region, two X cell classes nonetheless exist. A key unanswered question is whether the cells we have identified as nonlagged can ever be converted to the lagged mode by activation or inactivation of the suitable nonretinal afferents. On the other hand, it may be that all X cells can enter lagged response mode, and their ability to do so is a continuously distributed variable among X cells, which are thereby a single class. If so, then it may be that certain other traits, like axonal conduction velocity and morphology (10, 13), covary with this propensity towards lagged responses.

Just how parabrachial activation causes an X cell to switch into its nonlagged response mode from its lagged mode is unclear, but it is known that parabrachial axons exert a powerful influence on geniculate relay cells both directly and through local inhibitory circuits (for review, see refs. 1 and 2). More specifically, some of these axons are known to innervate relay X cells directly in complex relationships with retinal inputs (17), which may represent part of the morphological substrate for the phenomenon we have described. Also, acetylcholine, which seems to be the transmitter used by most parabrachial axons (18, 19), has dramatic effects on the membrane properties of geniculate relay cells recorded *in vitro* (20). The background for the kinds of effects we have described on response properties of geniculate neurons has thus been established.

Regardless of the underlying mechanisms for these effects, we have demonstrated a dramatic change in the receptive-field properties of certain geniculate cells by appropriate activation of a nonretinal pathway. So dramatic is this change

in response modes that, when first described, these modes were mistaken for completely different neuronal types. Given the anesthetized, paralyzed preparation and the limited activation of nonretinal afferents we employed, this may be the proverbial tip of the iceberg in terms of the broader ability of nonretinal afferents to alter retinogeniculate transmission.

We thank P. C. Murphy for helping with some of these experiments. This work was supported by Public Health Service Grants EY06610 and EY03038 and the Japan Ministry of Education.

1. Sherman, S. M. & Koch, C. (1986) *Exp. Brain Res.* **63**, 1–20.
2. Steriade, M. & Llinas, R. R. (1988) *Physiol. Rev.* **68**, 649–742.
3. Singer, W. (1977) *Physiol. Rev.* **57**, 386–420.
4. Burke, W. & Cole, A. M. (1978) *Rev. Physiol. Biochem. Pharmacol.* **80**, 105–166.
5. Guillery, R. W. (1971) *Vision Res. Suppl.* **3**, 211–227.
6. Wilson, J. R., Friedlander, M. J. & Sherman, S. M. (1984) *Proc. R. Soc. London Ser. B* **221**, 411–436.
7. Stone, J. (1983) *Parallel Processing in the Visual System* (Plenum, New York).
8. Sherman, S. M. (1985) *Prog. Psychobiol. Physiol. Psychol.* **2**, 233–313.
9. Shapley, R. & Lennie, P. (1985) *Annu. Rev. Neurosci.* **8**, 547–583.
10. Mastronarde, D. N. (1987) *J. Neurophysiol.* **57**, 357–380.
11. Mastronarde, D. N. (1987) *J. Neurophysiol.* **57**, 381–413.
12. Humphrey, A. L. & Weller, R. E. (1988) *J. Comp. Neurol.* **68**, 429–447.
13. Humphrey, A. L. & Weller, R. E. (1988) *J. Comp. Neurol.* **68**, 448–468.
14. Sur, M. & Sherman, S. M. (1982) *J. Neurophysiol.* **47**, 869–884.
15. Bloomfield, S. A. & Sherman, S. M. (1987) *J. Physiol. (London)* **383**, 653–692.
16. Uhlrich, D. J., Cucchiari, J. B. & Sherman, S. M. (1988) *J. Neurosci.* **8**, 4565–4575.
17. Cucchiari, J. B., Uhlrich, D. J. & Sherman, S. M. (1988) *J. Neurosci.* **8**, 4576–4588.
18. De Lima, A. D. & Singer, W. (1987) *J. Comp. Neurol.* **259**, 92–121.
19. Smith, Y., Pare, D., Deschenes, M., Parent, A. & Steriade, M. (1988) *Exp. Brain Res.* **70**, 166–180.
20. McCormick, D. A. & Prince, D. A. (1987) *J. Physiol. (London)* **392**, 147–165.