JOURNAL OF NEUROPHYSIOLOGY
Vol. 76, No. 3, September 1996. *Printed in U.S.A.*

Metabotropic Glutamate Receptors Switch Visual Response Mode of Lateral Geniculate Nucleus Cells From Burst to Tonic

DWAYNE W. GODWIN, J. WILLIAM VAUGHAN, AND S. MURRAY SHERMAN
Department of Neurobiology, State University of New York, Stony Brook, New York 11794-5230

SUMMARY AND CONCLUSIONS

1. Metabotropic glutamate receptors (mGluRs) on relay cells of the lateral geniculate nucleus appear to be activated exclusively by cortical inputs. We thus sought to manipulate these receptors in an effort to gain insight into the possible role of the corticogeniculate pathway. We used in vivo recording and pharmacological techniques in cats to activate or inactivate these receptors on geniculate neurons while analyzing their response properties.

2. Iontophoretic application of the mGluR agonist 1-amino-cyclopentane-1,3-dicarboxylic acid (ACPD) to X and Y cells in the geniculate A laminae diminished or abolished burst activity characteristic of low-threshold Ca^{2+} spikes. This was accompanied by pronounced changes in the visual response, including a decrease in signal detectability as measured with receiver operating characteristic curves.

3. ACPD effects appear specific to mGluRs, because a specific antagonist of ionotropic glutamate receptors (iGluRs) failed to affect the ACPD-evoked responses, and antagonists of ACPD failed to affect iGluR-mediated responses. We found that 3,5-dihydroxyphenylglycine, an agonist reported to be specific for phosphatidylinositol (PI)-linked mGluRs, had effects similar to those of ACPD, implying that these effects are mediated by PI-coupled mGluRs. Furthermore, antagonists reported to be effective against PI-linked mGluRs were effective in antagonizing the ACPD-mediated effects, and substances reported to be agonists to mGluRs coupled to the adenosine 3′,5′-cyclic monophosphate cascade did not affect neuronal responses on their own. These data, when added to our preliminary anatomic data, indicate that the receptor responsible for the observed effects may be mGluR1, or a functionally equivalent mGluR.

4. Activation of mGluRs produces changes in geniculate relay cell activity consistent with depolarization of these cells seen during in vitro studies. Such membrane depolarization has been shown to control the activation state of a voltage-dependent Ca^{2+} conductance, and this, in turn, determines whether the relay cell fires in tonic or burst mode. Our data show that application of ACPD produces a shift in response mode from burst to tonic. Because response mode is an important characteristic of the geniculate relay and because the activation state of certain mGluRs, which helps determine response mode, may be controlled by corticogeniculate input, we conclude that an important function of this input is to provide a visuotopically discrete transition from burst to tonic response mode.

INTRODUCTION

The dorsal lateral geniculate nucleus is a dynamic relay of the visual information transmitted from the retina to primary visual cortex. It is a relay in the sense that most of the receptive field structure originating in the retina is transmitted through the lateral geniculate nucleus to cortex, but it is also dynamic in that visual information may be filtered or gated according to behavioral state or stimulus attribute (Livingstone and Hubel 1981; Norton and Godwin 1992; Sherman and Koch 1990; Singer 1977).

A property of relay cells that is important to this gating is their ability to respond to afferent input in one of two very different response modes (Jahnsen and Llinás 1984a,b; Steriade et al. 1993; Sherman and Koch 1986, 1990): tonic or burst.[1] The response mode depends on the activation state of a voltage-dependent Ca^{2+} conductance known as the low-threshold spike. At depolarized membrane potentials, this conductance is inactivated, and an incoming depolarizing input such as an excitatory postsynaptic potential (EPSP) leads to firing in tonic mode with a continuous stream of conventional Na^+/K^+ action potentials. At hyperpolarized levels, the conductance is deinactivated, or primed, and an EPSP produces a low-threshold spike due to Ca^{2+} entry; typically riding its crest is a high-frequency burst of 2–10 action potentials with interspike intervals $\leq$4 ms, and these bursts are separated by $\geq$50–100 ms. The activation state of the low-threshold spike also has a time dependency: roughly 50–100 ms of continuous hyperpolarization is needed to switch the state from inactivated to deinactivated, and a similar period of depolarization is needed to switch states in the opposite direction. We have shown that geniculate cells in burst mode detect and signal the presence of visual stimuli more reliably than when in tonic mode, but at the expense of response linearity that is important for accurate and detailed analysis of visual form (Guido et al. 1995).

Certain nonretinal inputs to geniculate relay cells are capable of depolarizing these cells, inactivating the low-threshold spike to promote tonic firing, and thereby affecting retinogeniculate transmission. The best example of this to date is the cholinergic input arising from the parabrachial region of brain stem. Activation of this pathway, or activation of cholinergic receptors on lateral geniculate nucleus cells, provides enough prolonged depolarization of relay neurons to switch them dramatically from burst to tonic mode (Eysel et al. 1986; Francesconi et al. 1988; Lu et al. 1993; McCormick and Prince 1987). To the extent that other nonretinal inputs may produce a long-lasting depolarization of relay

[1] "Tonic" used in this sense refers to a response mode of a geniculate relay cell, and here it is paired with "burst." X and Y cells, the relay cell types found in the A laminae of the cat's lateral geniculate nucleus, display both response modes. This should not be confused with another, archaic use of "tonic" when paired with "phasic" to refer to a cell type: "tonic" for X and "phasic" for Y. Throughout this account, we use "tonic" only to refer to response mode and not to cell type.

cell membrane potential, they may also promote tonic responses.

An excellent candidate for this is the axons from layer 6 of visual cortex, which provides the largest synaptic input to geniculate relay cells (see Sherman and Koch 1986, 1990). There is in vivo and in vitro evidence that this corticogeniculate pathway is glutamatergic and depolarizing (McCormick and von Krosigk 1992; Sharfman et al. 1990). Both *N*-methyl-D-aspartate (NMDA) and 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propanoate (AMPA) receptors are involved. These receptors are ionotropic glutamate receptors (iGluRs) and they directly gate ionic channels to produce fast EPSPs. Scharfman et al. (1990) showed that both retinal and cortical axons activate both AMPA and NMDA receptors to produce EPSPs on geniculate cells. A problem with the suggestion that the corticogeniculate input may control tonic versus burst response modes via these iGluRs is their dynamics: the resultant EPSPs may be too fast to inactivate the low-threshold spike.

However, recent evidence suggests a neuromodulatory role for glutamate through metabotropic glutamate receptors (mGluRs), which act on ion channels through intracellular, second-messenger pathways. EPSPs resulting from activating certain mGluRs are much more prolonged and seem well suited to controlling response mode. There are at least eight subtypes of mGluRs, which are segregated into three groups on the basis of sequence similarity, intracellular second-messenger involvement, and agonist sensitivity (for details, see Duvosin et al. 1995; Watkins and Collingridge 1994): group I includes mGluR1 and mGluR5, which are coupled via phosphatidylinositol (PI)-specific phospholipase C to PI hydrolysis and intracellular Ca^{2+} mobilization; group II includes mGluR2 and mGluR3, which are negatively coupled via adenylate cyclase to forskolin-stimulated adenosine 3′,5′-cyclic monophosphate (cAMP) formation; and group III includes mGluR4, mGluR6, mGluR7 and mGluR8, which are also negatively coupled to cAMP formation but demonstrate a different agonist sensitivity from mGluR2 and mGluR3 (Duvosin et al. 1995; Watkins and Collingridge 1994). Other second-messenger systems may also be involved with these mGluRs (Conn et al. 1994), but those described above distinguish the three groups. All are activated by the mGluR agonist 1-amino-cyclopentane-1,3-dicarboxylic acid (ACPD). Recently, a series of phenylglycine derivatives has been shown to be effective agonists or partial antagonists to mGluRs (Birse et al. 1993), with varying degrees of subtype specificity. In ventrobasal thalamus, Salt and Eaton (1994) used some of these to demonstrate effective antagonism of excitatory responses to ACPD.

McCormick and von Krosigk (1992) showed in the guinea pig lateral geniculate nucleus that application of ACPD or activation of mGluRs through the corticogeniculate (but not the retinogeniculate) pathway resulted in a long-lasting EPSP (on the order of several seconds) due to the decrease of a resting K^+ conductance. The evidence that activation of mGluRs on geniculate relay cells leads to very slow EPSPs and that such activation occurs primarily, if not solely, via corticogeniculate inputs suggests the possibility that this input may be well able to control response mode. Our preliminary in vitro data confirm the involvement of this receptor system in cat lateral geniculate nucleus, and confirm that this slow EPSP promotes the expression of tonic response mode by a membrane depolarization that inactivates the low-threshold spike (Zhou et. al 1994).

We wished to extend these studies of activation of mGluRs on geniculate neurons. Previous studies have relied on in vitro methodology, so we concentrated on activating mGluRs in geniculate cells in the intact cat and determining how such activation affected responses and response mode during visual stimulation. To the extent that the mGluR activation is exclusive to the corticogeniculate pathway, as has been reported from in vitro experiments (McCormick and von Krosigk 1992), we hoped that this approach could offer new insights into the functioning of the corticogeniculate pathway. Preliminary results of this study have been reported in abstract form (Godwin et al. 1994).

METHODS

Preparation

We adopted previously published methods (Godwin 1993; Guido et al. 1992, 1995; Holdefer et al. 1989; Lo et al. 1991; Lu et al. 1992), briefly outlined below, to perform experiments on adult cats. We anesthetized the cats initially with 3.5% halothane and maintained anesthesia after surgery with 0.5–1.0% halothane in a 70:30 mixture of N_2O:O_2. The cats were paralyzed with gallamine triethiodide (5.0 mg) and were artificially respired through a tracheal cannula. We maintained paralysis with drugs delivered through a cannulated femoral vein (gallamine triethiodide, 3.6 mg/h; and tubocurarine, 0.7 mg/h). Wound margins and pressure points were treated with a topical anesthetic. We then placed the cats in a stereotaxic apparatus for recordings. Rectal temperature, heart rate, and end-tidal CO_2 were continuously monitored and maintained within normal physiological limits. At the end of the recording session, the cats were killed with an overdose of barbiturates without ever recovering from anesthesia.

Access to the lateral geniculate nucleus was obtained though a craniotomy (5.0 mm diam) centered at A5.0, L9.0. A pair of insulated tungsten electrodes (500-μm exposed tips, 4-mm separation) were lowered to straddle the optic chiasm through a second craniotomy centered on the midline at A13.0. We orthodromically activated geniculate neurons through these electrodes with the use of single stimuli (0.1 ms, 1 Hz, 100–500 μA) to assist in identifying different geniculate neuronal classes (see below).

After dilating the pupils with atropine sulfate, we protected the corneas with contact lenses selected by retinoscopy to focus the retinas on stimuli presented on a frontal tangent screen placed 57 cm in front of the eyes. We used a fiberoptic light source to reflect the tapetum onto the tangent screen (Pettigrew et al. 1979), permitting us to plot retinal landmarks (including the optic disk, area centralis, and major retinal blood vessels). We recorded from single neurons in the geniculate A laminae and delivered drugs with a tungsten-in-glass recording electrode (impedances 8–14 MΩ) combined with a multibarrelled drug pipette (Godwin 1993). Neuronal activity was amplified, displayed on an oscilloscope, voltage window discriminated, and stored on computer as spike arrival times with a resolution of 0.1 ms.

Visual stimulation and classification of geniculate cells

Neuronal receptive field position, on- or off-center type, size, and ocularity were initially determined by plotting activity evoked from small spots of light projected onto the tangent screen. The tangent screen was then replaced with a Tektronix 608 oscilloscope monitor for the presentation of visual stimuli under computer control. Counterphase modulated sinusoidal gratings were used to test

linearity of spatial summation to assist with cell classification (see below).

We used the oscilloscope to present dark or light spots centered on the receptive field of each geniculate cell, dark spots for off-center cells and light spots for on-center ones. The spots were presented on a cathode ray tube under computer control. The background was held at a luminance of 15 cd/m^2, bright spots were typically 60 cd/m^2, and dark spots were typically 3.7 cd/m^2. These values provide a contrast of 0.6 for both bright and dark spots. Occasionally spots of less contrast were used, but we noted little difference in responses, and thus the data presented here reflect responses to the bright and dark spots as indicated.

We classified all neurons as X or Y like with the use of a battery of tests, including latency to electrical stimulation from optic chiasm, linearity of spatial summation, center size, and the response of the surround to a large, rapidly moving stimulus of opposite contrast to the receptive field center (Shapley and Lennie 1985; Sherman 1985). We classified burst responses due to low-threshold spikes from extracellularly recorded spike arrival times with the use of previously published criteria (Guido et al. 1995). In brief, a response was classified as a low-threshold burst if its constituent action potentials were ≤4 ms apart, with the first spike in a burst preceded by a silent period of ≥100 ms. We summarized burst activity for each cell and under each drug condition with a burst index, which is simply the proportion of stimulus presentations that evoked a low-threshold burst (Guido et al. 1992, 1995; Lu et al. 1992). This index could thus range between 0 and 1.

Pharmacology

We iontophoretically applied the following agonists and antagonists at pH 8.0, delivered as anions, through a multibarrelled pipette (Godwin 1993) at the concentrations indicated in parentheses: trans-(1S,3R),-1-amino-1,3-cyclopentanedicarboxylic acid (1S,3R-ACPD; 30 mM); trans-(±)-ACPD (trans±ACPD; 30 mM); s-4-carboxy-3-hydroxyphenylglycine (4C3HPG, 60 mM); NMDA (100 mM); (±)-2-amino-5-phosphonopentanoic acid (AP5, 50 mM); 3′5′-dihydroxyphenylglycine (DHPG, 30 mM); s-4-carboxyphenylglycine (4CPG, 60 mM); quisqualate (25 mM); and 6,7-dinitroquinoxaline-2,3-dione (DNQX, 20 mM). Conventional controls were performed to preclude nonspecific effects of pH and current, including iontophoretic application of vehicle solutions of identical pH (but devoid of drug) and the use of circuitry that balanced to zero net currents occurring at the tips of the iontophoretic pipette. We recorded neuronal signals through a tungsten-in-glass electrode affixed 30–60 μm in advance of the iontophoretic pipettes (Godwin 1993).

In addition to antagonist activity at group I mGluRs, 4CPG and 4C3IIPG also have reported agonist activity at group II mGluRs (specifically mGluR2) as expressed in Chinese hamster ovarian cells (Hayashi et al. 1994). However, we used these substances to probe group I mGluRs for three reasons. First, they are known to antagonize group I mGluRs, and 4CPG has been suggested to be specific to mGluR1 (Joly et al. 1995). Second, possible group II agonist effects could be probed by testing these substances without ACPD. Third, ACPD is also an agonist to group II mGluRs, and thus any excitatory or inhibitory effect produced by ACPD through group II mGluRs should be augmented by 4CPG and 4C3HPG, not diminished, and this can be tested. It is possible that group II agonist effects occur that are invisible to our recording electrode through second-messenger involvement, but such hypothetical effects are beyond the scope of the current study.

Receiver operating characteristic curve analysis

In addition to other standard response measures (e.g., firing rate and burst index), we generated receiver operating characteristic (ROC) curves for responses of geniculate neurons. These curves provide a criterion-free, nonparametric estimate of detectability, or how well a neuron discriminates visually driven (signal) from maintained activity (noise). The details of this analysis technique have been presented elsewhere (Guido et al. 1995; Holdefer et al. 1989; Macmillan and Creelman 1991; Wilson et al. 1988). In brief, we develop ROC curves as follows. We determine the cumulative probability distributions of activity occurring in two sampling periods, 500 ms in duration, one occurring just before the presentation of the visual stimulus (maintained activity), the other occurring just after the onset of the stimulus (visually driven activity). We determine these distributions for all possible criterion levels present in our data and plot these against one another at each possible criterion level. The possible criterion levels range from the least stringent of no spikes occurring to the most stringent of the largest number of spikes seen in any epoch. It follows that the probability of the response exceeding the least stringent criterion will be very high, approaching 1, that the probability for the most stringent will be very low, approaching 0, and that intermediate criterion values will lead to intermediate probability values. The plotting of these various probability values for each criterion generates the ROC curve. The area under the ROC curve, or ROC area, may vary between 0 and 1, although in practice it varies between 0.5 and 1, and it is monotonically related to detectability. An area of 1 denotes perfect detectability, and an area of 0.5 denotes an inability to distinguish signal from noise. The validity of the technique does not depend on assumptions about the nature of the underlying distributions (Guido et al. 1995; Holdefer et al. 1989; Macmillan and Creelman 1991; Wilson et al. 1988). We plotted ROC curves from data collected under each drug treatment condition noted above.

RESULTS

We studied the visual responses of 61 cells (35 X and 26 Y cells; 33 on-center and 28 off-center cells) in the A laminae of the lateral geniculate nucleus. Of these, 17 were also tested with one of two antagonists effective against excitatory mGluR activation. Seven of these were also tested with iGluR agonists and antagonists. The receptive fields of the recorded neurons were within 30° of the area centralis. The effects to be reported here were not selective for cells identified as X versus Y or on-center versus off-center, and we thus pooled data across all cells for the analyses.

Effects on spontaneous activity

Of our total sample of 61 cells, 14 exhibited spontaneous activity exclusively in tonic mode with no evidence of bursting, and thus 47 cells showed at least some spontaneous activity in burst mode. The effects of iontophoretic application of ACPD (either trans±ACPD or 1S,3R-ACPD) took ~3 min to become established. The clearest and most consistent effect of ACPD application was seen on the 47 cells showing at least some burst firing: there was a strong tendency during spontaneous activity to shift response mode from burst to tonic. Figure 1 shows a typical example. In the control condition before ACPD application (Fig. 1*A*), the cell shows frequent spontaneous bursts. Also, the interspike interval distribution revealed a large, sharp peak at very short intervals (≤4 ms) representing the bursts. ACPD application (Fig. 1*B*) completely eliminated burst activity, and the interspike interval distribution was without any obvious peak. Each cell that showed at least some spontaneous

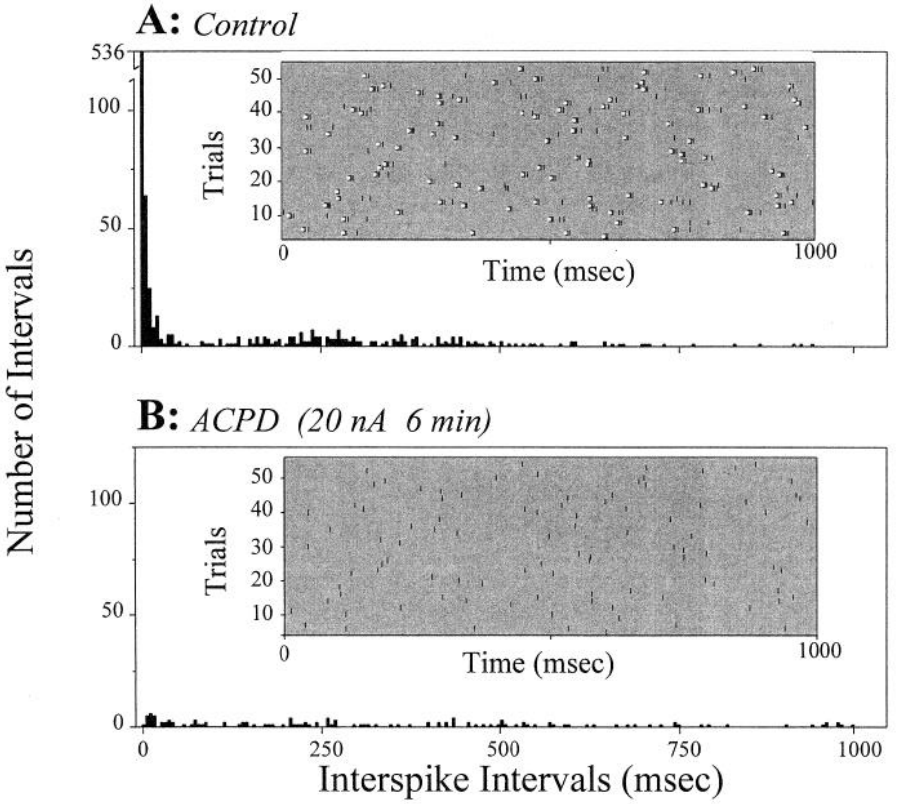

FIG. 1. 1-Amino-cyclopentane-1,3-dicarboxylic acid (ACPD) diminishes spontaneous low-threshold spike activity. The histogram of interspike intervals shows the large peak for intervals ≤4 ms typical of bursts (see METHODS). *Inset*: spike raster of 50 individual epochs; each spike is indicated by a tick mark, and each burst of spikes is further indicated by a small white dot. *B*: spontaneous activity showing lack of bursting during ACPD application. Note the absence of the early peak in the interspike interval histogram and the complete lack of bursts in the raster display.

bursting in the control condition had its burstiness reduced after ACPD application. Presumably the depolarization caused by activation of the mGluRs (McCormick and Von Krosigk 1992) was often sufficient to inactivate the low-threshold spike underlying the bursts of action potentials.

Thus the main tendency of ACPD application was to reduce burst responses and increase tonic ones. Note that this refers not to overall responsiveness but simply to the subset of action potentials in burst or tonic mode.

Other than this relative effect on burst and tonic responsiveness, there was often little effect on spontaneous activity observable immediately after application of this drug. Effects were seen after tens of seconds. In most cells, ACPD application resulted in a modest increase in spontaneous activity, but in others, there was little change in the activity level, and in some cases, ACPD caused a modest reduction in spontaneous activity (see below), a feature never seen with application of iGluR agonists. This is in contrast to AMPA or NMDA receptor activation, which caused a noticeable peak in firing within a second or two of agonist delivery and which could produce eventual depolarization block (not illustrated). Activation of these iGluRs opens channels for various cations to flow into the cell, and the reversal potentials for these cations are quite positive with respect to the resting membrane potential (Mayer and Westbrook 1987). This leads to powerful depolarization, which is apparently often strong enough to directly activate action potentials, independent of retinal input. However, activation of mGluRs by ACPD produces a much weaker depolarization, because this results from a reduced K^+ leak current, and this can only provide a slightly more depolarized resting potential. This weaker depolarization is evidently insufficient in most cases to directly excite action potentials on its own, but by moving the membrane potential closer to threshold, it raises the probability that EPSPs due to activation of iGluRs will fire action potentials. Also, in some cases, the slight depolarization may switch the cell from fairly active burst activity to tonic firing, but at a relatively hyperpolarized level for tonic mode that is reflected in a lower overall firing rate (see below).

Effects of ACPD application on visually driven activity

ACPD had several dose-dependent effects on visually driven responses. In tandem with decreases in burst firing, we typically observed increases in both spontaneous and the sustained portion of visually driven activity with increasing iontophoretic currents and application times. This is illustrated in Fig. 2, which also shows the effect of drug application on the burst index (see METHODS). Note, however, that although increasing ACPD application produced a lower burst index, and that as a result the sustained portion of the response increased, the initial, abrupt peak in response to spot onset actually decreased. In other words, the switch from burst to tonic firing caused by ACPD promoted a smaller initial peak response but a larger sustained response to a flashing spot. However, in most cases, when we considered the 500-ms period after onset of the stimulus, ACPD application increased the response (see below for details). These effects recovered within 3 min. Figure 3 shows further that both 1S,3R-ACPD (the active enantiomer of trans-ACPD) and DHPG (an agonist reported to be specific to

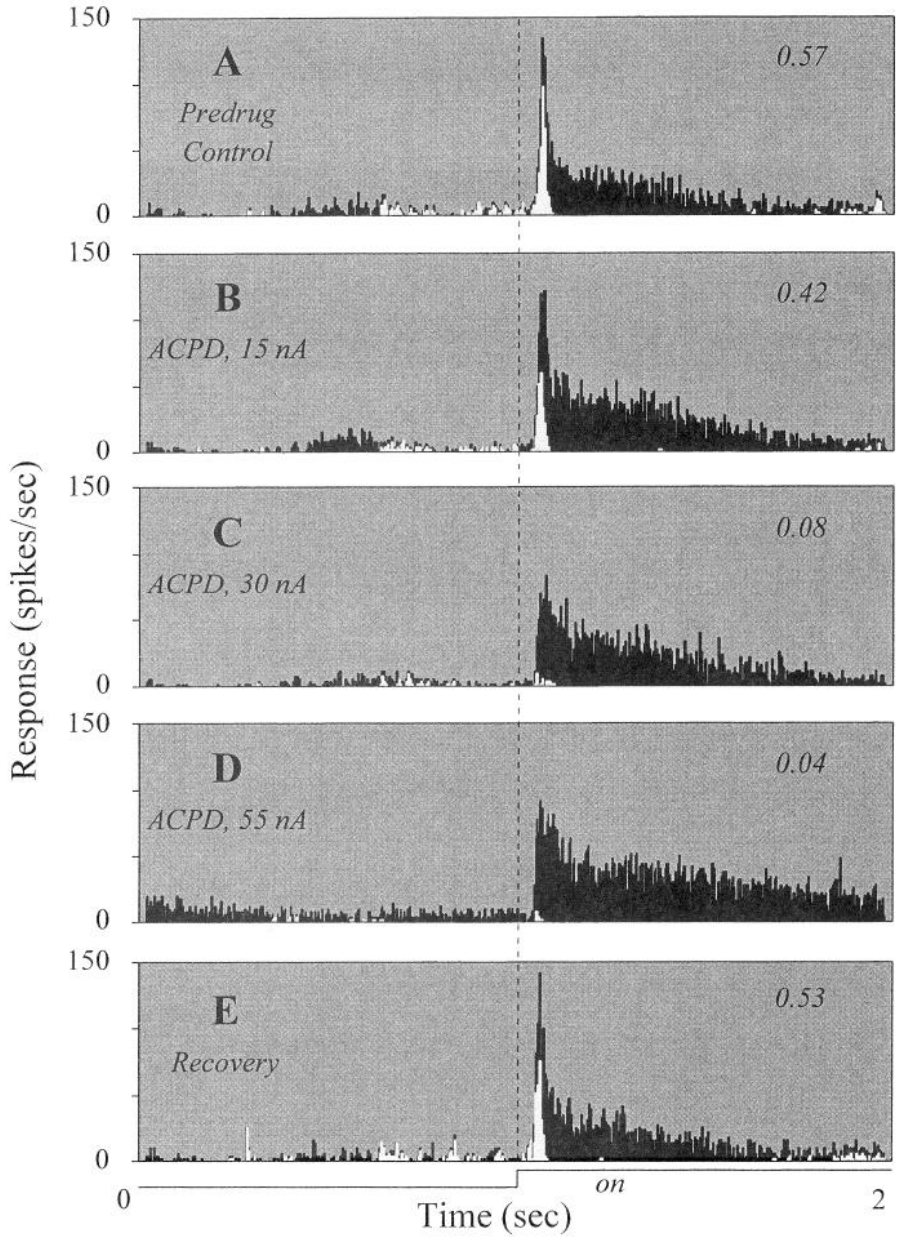

FIG. 2. Effect of application of metabotropic glutamate receptor (mGluR) agonist, trans-ACPD, on the activity of a geniculate Y cell. Unless otherwise specified in this and succeeding figures, agonist and antagonist are delivered iontophoretically for 5 min before and during the period the responses are obtained for analysis. Shown are the cell's responses to a spot of light with a contrast of 0.6 flashed on and off in the receptive field center (see vertical dashed line and trace at *bottom* for on and off phases of the stimulus). The solid histogram in each panel represents all spikes, and the white histogram represents the subset of spikes present in burst mode responses. The burst index is given in the *top right corner of each panel* (see text). The binwidth for these and all other histograms in succeeding figures is 5 ms. Each histogram represents data recorded in sequence from the same cell. *A*: control response before any agonist is delivered. *B*: response after ACPD was delivered with a current of 15 nA. *C*: response after trans-ACPD was delivered with a current of 30 nA. *D*: response after trans-ACPD was delivered with a current of 55 nA. *E*: control response 3 min after delivery of trans-ACPD is terminated. Note that, as the iontophoretic current increased to deliver more trans-ACPD, the cell's burstiness decreased, the initial transient response to the spot decreased, and the sustained component of the response increased. These effects recovered within 3 min.

PI-coupled mGluRs; (Schoepp et al. 1994) had similar, reversible effects to those shown in Fig. 2.

Of our cell sample, the same 14 cells that showed only tonic firing during spontaneous activity also responded to flashing spots exclusively in tonic mode with no evidence of bursting, and the same 47 cells with some bursting during spontaneous activity also showed at least some visually evoked responses in burst mode. The scatter plot in Fig. 4*A* shows that ACPD reduced the burst index in 38 of the 47 cells (these points fall below the line of slope 1), and for the population, this effect is statistically significant ($P < 0.001$ on a Sign test). Figure 4*B* shows further that the effectiveness of ACPD in eliminating burst firing was related to the burstiness of the cell when the drug was applied. These two variables are significantly correlated ($r = -0.95$; $P < 0.001$). The net effect of ACPD was thus to promote tonic firing in cells that were in burst mode, presumably by depolarizing them and inactivating the low-threshold spike underlying burst responses. The minimal effects on cells responding chiefly in tonic mode suggests that these cells were already somewhat depolarized.

Specificity of the ACPD effect

ACPD is a specific agonist for mGluRs (Palmer et al. 1989; Watkins and Collingridge 1994). However, there are suggestions from other systems that mGluRs may modulate NMDA receptor function (e.g., Colwell and Levine 1994). We thus felt it important to verify that the measured drug effects did not result from either direct cross reactivity of the putative agonist with other iGluRs or indirect modulation of other iGluRs through intracellular pathways. We verified

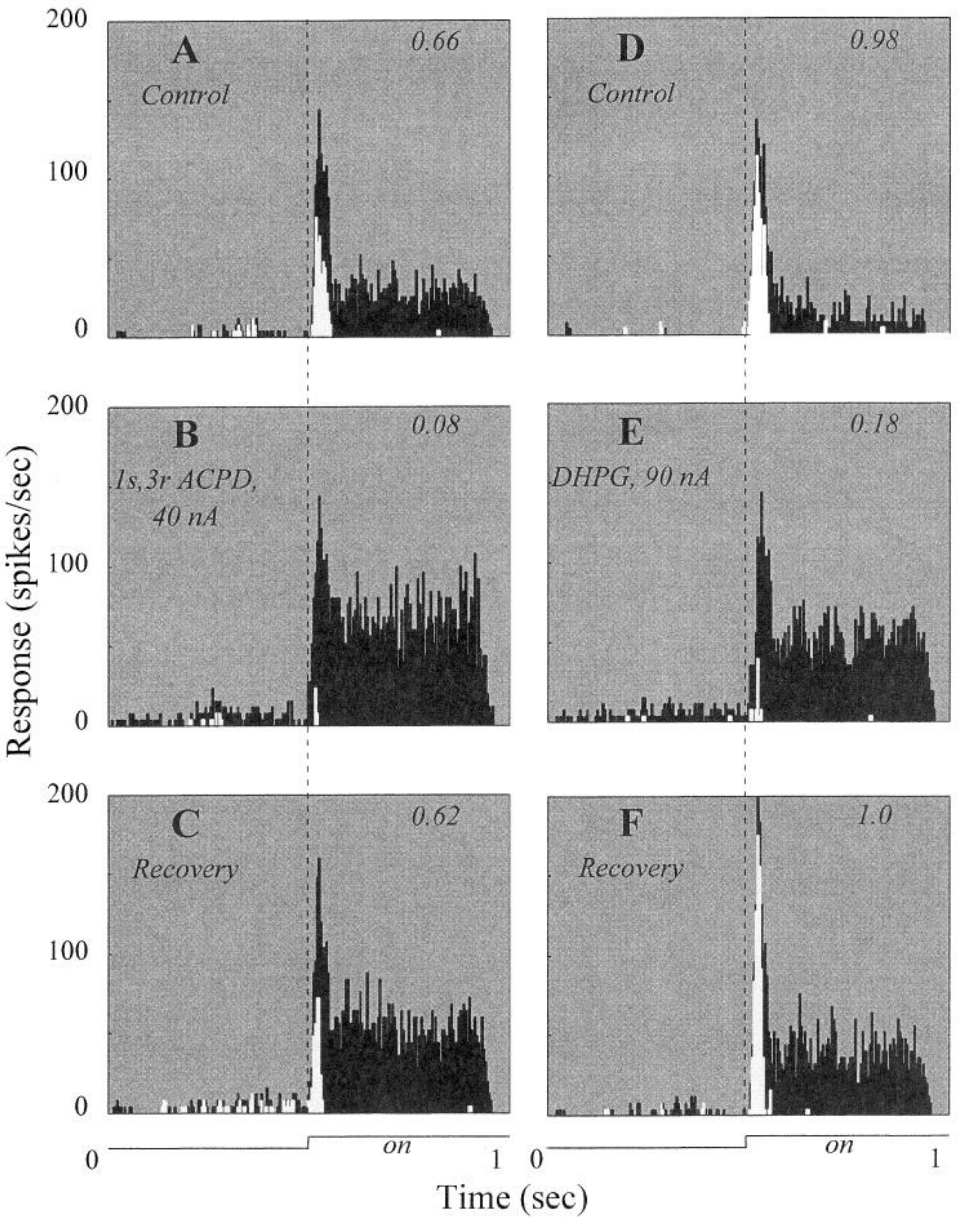

FIG. 3. Effects of application of mGluR agonists on an off-center geniculate Y cell; conventions as in Fig. 2. The stimulus was a dark spot of contrast of 0.6 centered on the receptive field. Note that these agonists produced effects identical to those illustrated in Fig. 2. *A–C*: predrug control (*A*), drug application (*B*), and postdrug recovery (*C*) of trans-(1S,3R),-1-amino-1,3-cyclopentanedicarboxylic acid (1S,3R-ACPD), the active enantiomer of trans-ACPD. *D–F*: predrug control (*D*), drug application (*E*), and postdrug recovery (*F*) of 3′5′-dihydroxyphenylglycine (DHPG), an mGluR agonist reported to be specific to the mGluRs coupled to phosphatidylinositol (PI) hydrolysis.

for seven cells that the ACPD effect on geniculate neurons was independent of activation of NMDA (5 cells) or AMPA receptors (2 cells).

TEST OF NMDA RECEPTOR INVOLVEMENT. Possible NMDA receptor involvement was probed by achieving an NMDA response, antagonizing the response with concurrent application of APV, and then using that level of APV against the ACPD application at the same antagonist current effective against NMDA. This control experiment is shown in Fig. 5, which shows the response histograms of an X cell to a flashed spot under the drug conditions indicated in the *inset* of each plot, with each record taken at intervals of ~4 min. Both the entire response (black histograms) and the subset of action potentials residing in burst responses (white histograms) are shown. NMDA application alone does reduce burst firing, but not as dramatically as did ACPD application (Fig. 5, *B* and *F*). Also, although the effect of NMDA was blocked by adding AP5, a specific NMDA antagonist (Fig. 5*C*), this same antagonist has no effect on ACPD effects (Fig. 5, *J* and *K*). In no case was the ACPD response antagonized or diminished by the AP5 application, although 4CPG, an antagonist of PI-coupled mGluRs, did antagonize the ability of ACPD to switch responses from burst to tonic (Fig. 5*G*).

TEST OF AMPA RECEPTOR INVOLVEMENT. We did not follow exactly the same protocol as outlined in Fig. 5 for NMDA receptors to control for AMPA receptors, because in our hands, complete antagonism of AMPA receptors could effectively block retinogeniculate transmission, preventing assessment of effects on responses to the visual stimuli. Both NMDA and AMPA receptors are used for retinogeniculate transmission (Kemp and Sillito 1982; Kwon et al. 1991; Scharfman et al. 1990; Sillito et al. 1990), but apparently although antagonism of the NMDA receptors permits visual

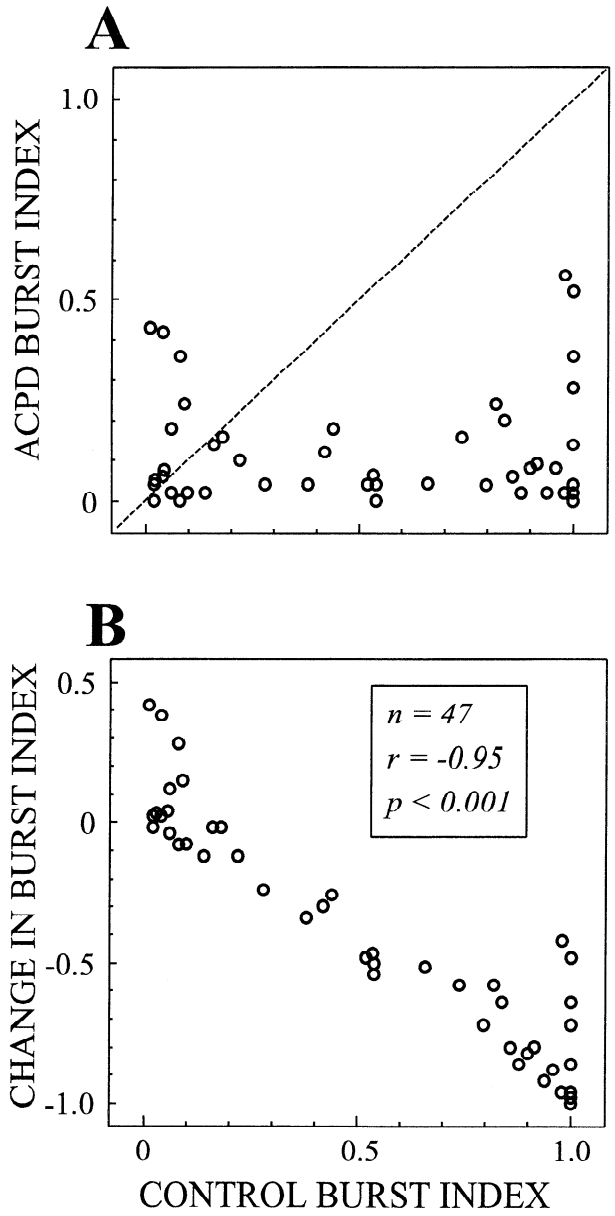

FIG. 4. ACPD effects on burst firing of geniculate cells. *A*: scatter plot showing for each cell the burst index before ACPD application vs. the burst index during ACPD application. The line of slope 1 is also shown. For the vast majority of cells, ACPD application reduces burst index. *B*: replotting of the data in *A* with the ordinate now representing the change in burst index. There is a highly significant, negative correlation between the initial burst index and the effects of ACPD applications, the major reduction in burst index tending to occur among those with higher initial burst indexes.

responses via the AMPA receptors, antagonism of the AMPA receptors prevents initial retinogeniculate depolarization of the relay cell, and this depolarization is needed by NMDA receptors to overcome their voltage-dependent Mg^{2+} block (Mayer and Westbrook 1987). Thus complete antagonism of AMPA receptors may serve to prevent both types of iGluRs from being activated by retinal axons.

We thus adopted the inverse strategy illustrated in Fig. 6, which, like Fig. 5, shows the total response via black histograms and the subset of the response due to low-threshold spiking in white histograms. Figure 6 illustrates several points that show specificity of the observed ACPD effects. The basic effect of ACPD in converting a response to the flashing spot from largely burst mode to largely tonic mode is illustrated in Fig. 6, *A–E*. Note that the ACPD-evoked responses were antagonized by iontophoretic application of the phenylglycine derivative 4CPG (Fig. 6*C*), but retinogeniculate transmission is not disrupted. Indeed, we have never been able to eliminate retinogeniculate transmission with the phenylglycine-derived antagonists. We have only been able to antagonize the effects of ACPD on firing rates and burst discharges. This is consistent with the reported physiological actions of excitatory mGluRs on the leak K^+ current, which does not seem to contribute directly to synaptic transmission. In contrast, antagonism of quisqualate-mediated responses with DNQX in the same cell (Fig. 6*H*) almost completely blocked retinogeniculate transmission, which argues that the effects of ACPD and DNQX occur through different mechanisms. Finally, Fig. 6, *M* and *N*, shows that the quisqualate evoked responses are not antagonized by application of 4CPG at iontophoretic currents sufficient to antagonize the ACPD-mediated effects, even after prolonged application of 4CPG (Fig. 6*N*). This does not rule out the possibility that quisqualate is an agonist at the mGluRs under study, but if so, quisqualate-evoked effects are much larger than those evoked by ACPD, and we were able to antagonize the ACPD effects with 4CPG.

Quantitative effects of ACPD on response levels

Figure 7 summarizes the population effects of ACPD application on both spontaneous and visually driven activity. Spontaneous activity (Fig. 7*A*) was measured as the average firing rate during the 500 ms immediately before onset of the flashing spot, and the rate for visually driven activity (Fig. 7*B*) was likewise measured during the 500 ms starting with spot onset. The scatter plots show the relationship between initial firing rates and rates after ACPD application. The majority of points are above the line of slope 1 for both spontaneous (56 of 61 cells) and visually driven activity (51 of 61 cells), and for the population, this increase during both response epochs is statistically significant ($P < 0.001$ on Sign tests). The *bottom histograms* show a similar result in a different fashion, comparing the response levels during ACPD application with that attained after recovery, which we took as ≥5 min after ACPD application was terminated. Again, the increases during ACPD application for both spontaneous and visually driven activity were statistically significant ($P < 0.001$ on Mann-Whitney *U* tests).

Influence of phenylglycine-derived antagonists on ACPD-mediated effects

As noted above, we used phenylglycine-derived compounds to antagonize ACPD (Watkins and Collingridge 1994). In several cells, we further assessed the effectiveness of two of these compounds, 4CPG and 4C3HPG, in reducing the ACPD-mediated effects. Although ACPD application made the response mode of many cells switch from predominantly burst to mainly tonic (e.g., Figs. 1–3, 5 and 6), Fig. 4 shows that the magnitude of this effect depends on the burst index in the control condition before ACPD application. Thus, by this measure, ACPD had little effect on cells

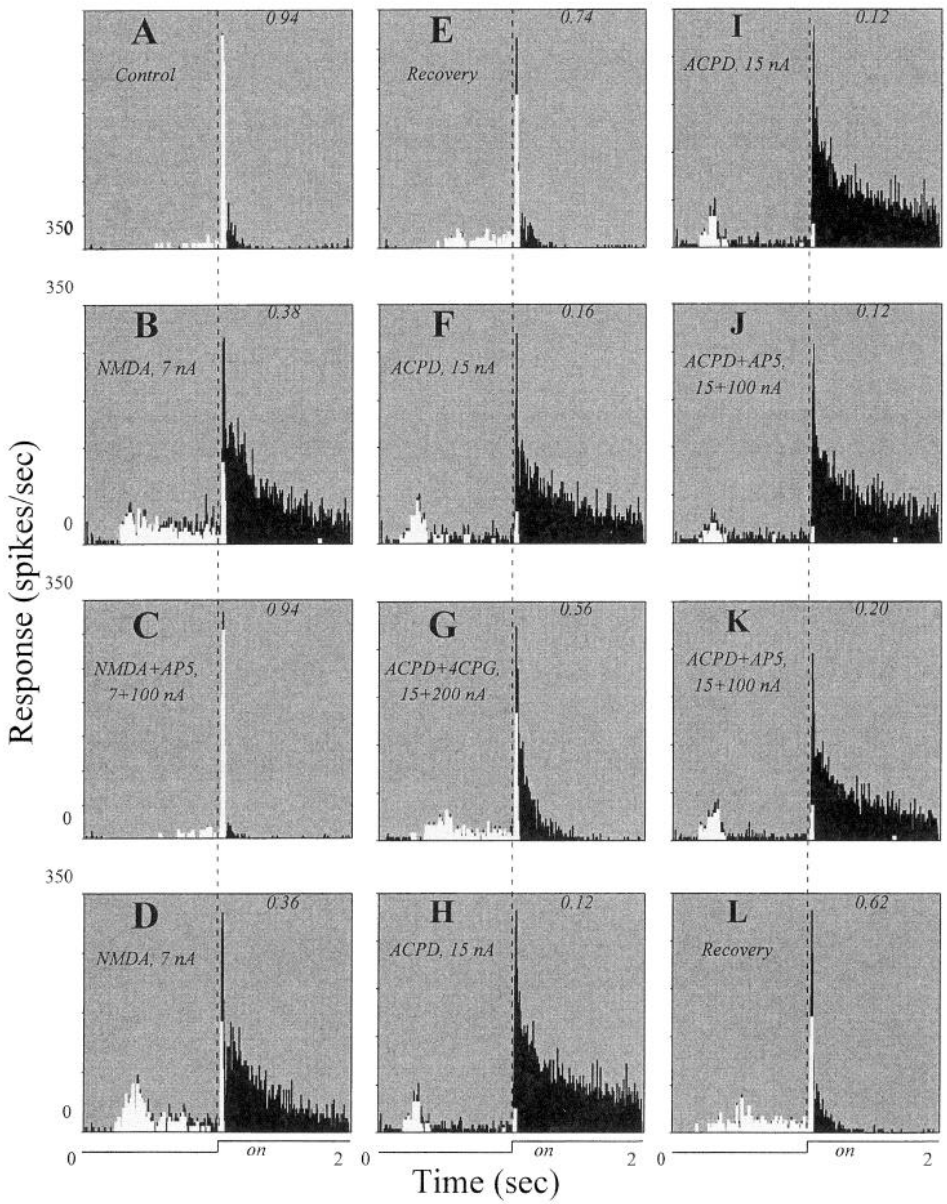

FIG. 5. Specificity of the ACPD effect in the presence of *N*-methyl-D-aspartate (NMDA) agonists and antagonists; conventions as in Fig. 2, and the cell illustrated is an on-center X cell responding to bright spot of contrast of 0.6 flashed in the center of the receptive field. *A*: predrug control response of cell, showing extensive bursting in response to the flashed spot. *B*: response during application of NMDA, which rendered the cell less bursty. *C*: response during antagonism of NMDA by (±)-2-amino-5-phosphonopentanoic acid (AP5), which restores original response mode. *D*: response to continued application of NMDA after removal of AP5, which restores responsiveness seen in *B*. *E*: recovery after cessation of NMDA administration. *F*: response during application of ACPD, which rendered the cell less bursty even than during NMDA application (*B*). *G*: antagonism of effects of ACPD application by s-4-carboxyphenylglycine (4CPG). *H*: response to continued application of ACPD after removal of 4CPG, which restores responsiveness seen in *G*. *I*: repeat of *H*. *J*: demonstration that AP5, which antagonizes the effect of NMDA (*C*), has no effect on ACPD application. *K*: demonstration that prolonged application of AP5 (7 min beyond *J*) has little further effect. *L*: recovery after cessation of all drug application. Note that the transient increase in neuronal discharge occurring in the spontaneous activity is composed primarily of rebound low-threshold spikes occurring just after the previous stimulus trial. These activity periods were not used in any of our population measures.

in tonic mode. A more general index of ACPD effects was the increase in mean firing rates for spontaneous and visually driven activity (Fig. 7). We used this measure to test the ability of the two phenylglycine derivatives to antagonize the effects of ACPD application. Figure 8 summarizes these results. Both 4CPG and 4C3HPG proved effective antagonists to the ACPD-mediated response increases, so Fig. 8 shows the pooled data from the tested cells, which were put through four conditions: the first (ACPD1) represents ACPD alone; the second (CPG) represents the addition of the antagonist; the third (ACPD2) represents another cycle of ACPD alone (i.e., after cessation of phenylglycine derivatives); and the fourth (Recovery) represents removal of agonist and antagonist, permitting the response to return to baseline. Because the phenylglycine compounds were applied concurrently with the ACPD in condition 2, there is some agonist rebound after antagonist treatment.

Because 4CPG and 4C3HPG may also have agonist activity at group II mGluRs (Hayashi et al. 1994), we tested these substances in separate control runs to determine whether we could detect changes in our physiological responses due to this possible agonist activity. We found that these substances had no significant effect on our response variables when applied in the absence of ACPD (not shown). Because ACPD is an agonist for both group I and group II mGluRs, coapplication of ACPD with 4CPG or 4C3HPG should yield additive effects if the excitation we observed were due to activation of a group II mGluR, but this did not occur.

Effects of ACPD application on signal detectability

We have previously used ROC analysis to show that as the response mode of geniculate cells becomes more tonic and less bursty, a switch occurs that is associated with mem-

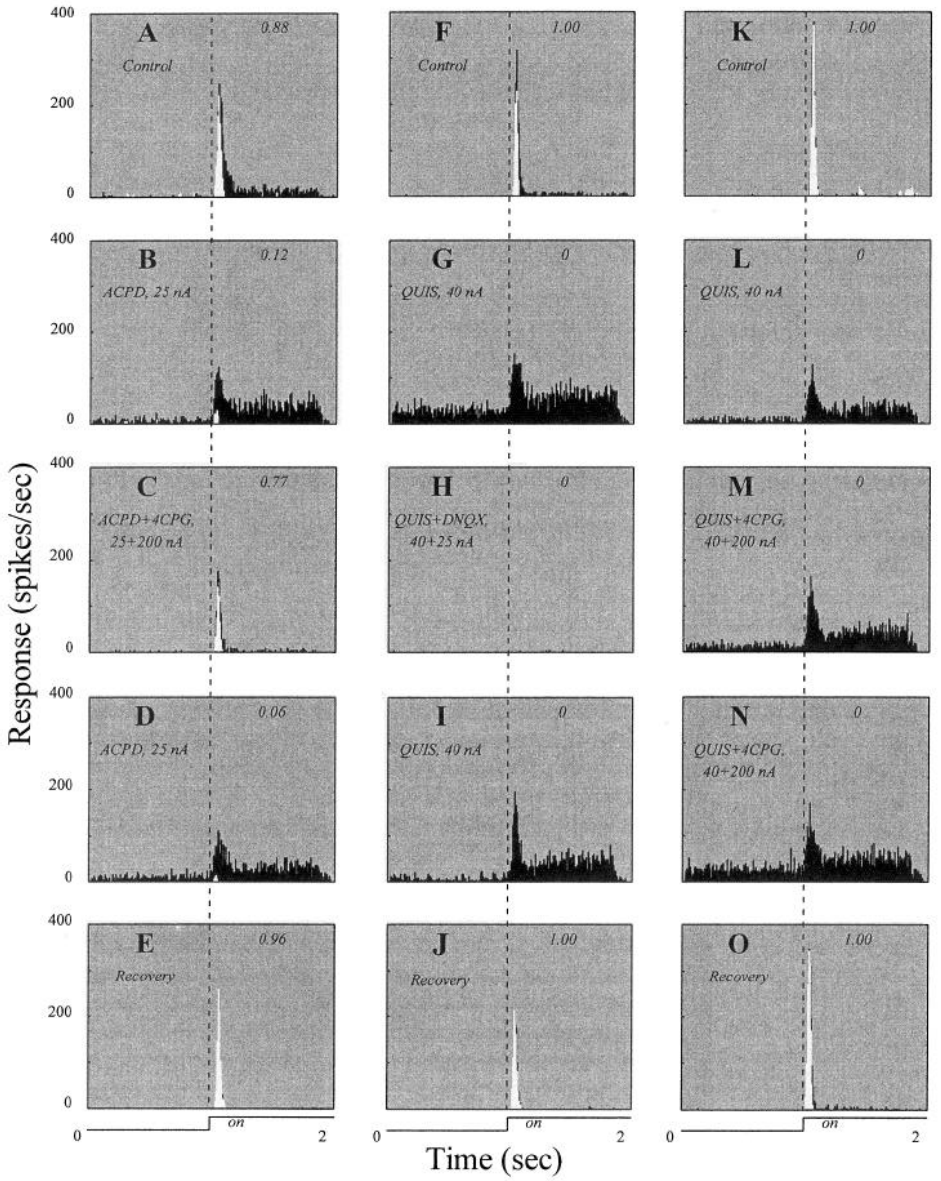

FIG. 6. Specificity of the ACPD effect in the presence of 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propanoate (AMPA) receptor agonists and antagonists; conventions as in Figs. 2 and 5, and the cell illustrated is an off-center Y cell responding to dark spot of contrast of 0.6 flashed in the center of the receptive field. *A*: response of cell during predrug control, showing extensive bursting in response to the flashed spot. *B*: response during application of ACPD, which rendered the cell much less bursty. *C*: response during antagonism of ACPD by 4CPG, which restores original response mode. *D*: response to continued application of ACPD after removal of 4CPG, which restores responsiveness seen in *B*. *E*: recovery after cessation of ACPD administration. *F*: continued recovery for an additional 5 min to ensure return to predrug control conditions. *G*: large application of an AMPA receptor agonist, quisqualate (QUIS), eliminates bursting. *H*: antagonism of quisqualate by the AMPA receptor antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX) completely eliminates all responses, presumably because without activation of AMPA receptors, retinal axons cannot discharge the neurons (see text). *I*: response to continued application of quisqualate after removal of DNQX, which restores responsiveness seen in *G*. *J*: recovery after cessation of ACPD administration. *K*: continued recovery for an additional 5 min to ensure return to predrug control conditions, as in *F*. *L*: large application of the AMPA receptor agonist quisqualate eliminates bursting, as in *G*. *M*: failure of 4CPG to antagonize effects of quisqualate. *N*: continued application of quisqualate and 4CPG for addition 5 min failed to affect response. *O*: postdrug recovery.

brane depolarization. These cells also become less able to detect stimuli because they exhibit decreases in the areas of their ROC curves (Guido et al. 1995). It appeared that this was due chiefly to an increase in spontaneous activity. Because ACPD application causes a switch from burst to tonic response mode, we anticipated that this would also be associated with a decrease in signal detectability. This indeed occurred. Figure 9 shows a typical example of this for an on-center Y cell. Iontophoretic application of ACPD produced an increase in response rate that was larger for spontaneous than for visually driven activity, and, as in other cells, also switched the cell from mainly burst to predominantly tonic firing. The *right column* shows that a decrease in the area under the ROC curve occurred in tandem with these other response changes. The phenylglycine derivative 4CPG antagonized the ACPD effect on each of these variables.

Figure 10*A* shows that the decrease in ROC area, and thus the decrease in signal detectability, caused by ACPD application was true for the population, because 46 of the 61 cells exhibited such a decrease ($P < 0.001$ on a Sign test). This figure shows ROC area of the ACPD treated cells plotted against the areas measured in the control condition. We found that four factors were associated with these decreases in ROC area. First, Fig. 10*B* shows that the ratio of visually driven activity (Fig. 7*B*) to spontaneous activity (Fig. 7*A*) tended to decrease with ACPD application for 47 of the 61 cells ($P < 0.001$ on a Sign test), and the average reduction in this ratio was >10 ($P < 0.001$ on a Mann-Whitney U test). That is, spontaneous activity increased with ACPD application proportionately more than did visually driven activity (see Fig. 7, *A* and *B*), and the reduced ratio associated with ACPD application was consistent with the reduced signal detectability. Second, and consistent with Fig. 10*B*, Fig. 10*C* shows that the decrease in ROC area was significantly correlated with increased spontaneous activity ($r = -0.58$, $P < 0.001$) but not with increases in

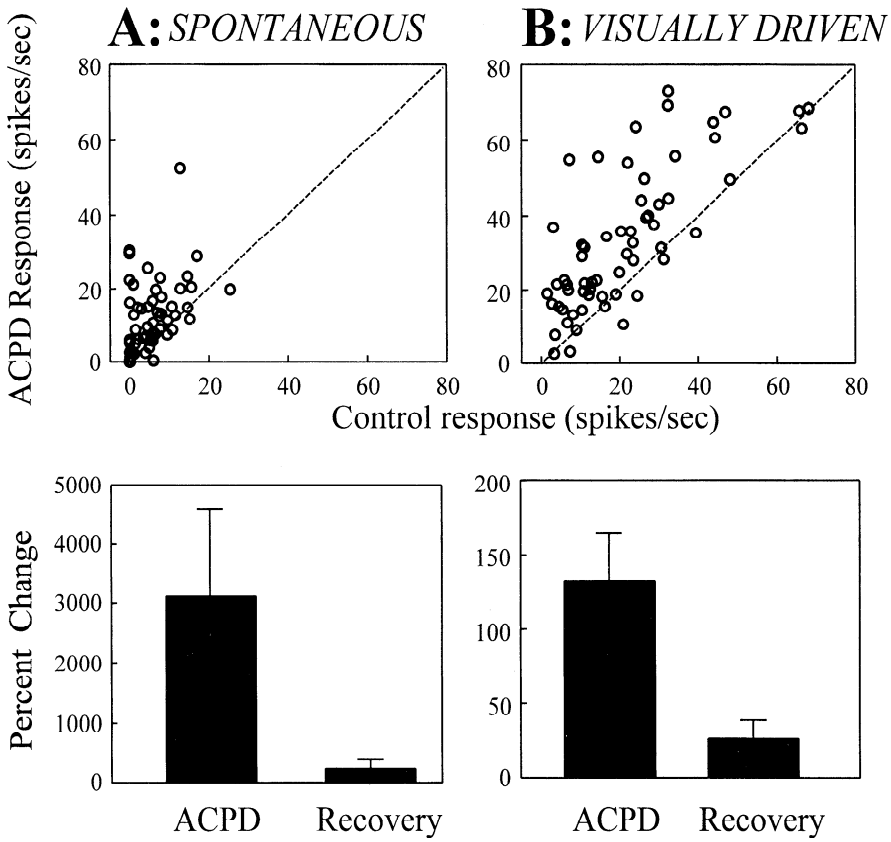

FIG. 7. ACPD effects on spontaneous and visually driven activity. *Top*: scatter plot of each cell's response level before ACPD application vs. its response level during ACPD application; the line of slope 1 is also shown. *Bottom*: % change in mean response level and SE of that change during ACPD application (ACPD) and after its termination (Recovery). Note that, although ACPD increased both spontaneous and visually driven activity, the increase of the former was much greater. *A*: spontaneous activity. *B*: visually driven activity.

visually driven activity ($r = -0.02$, $P > 0.1$; not illustrated). Third, Fig. 10*D* shows that the decrease in the area under the ROC curve was significantly correlated with the drop in burst index ($r = +0.50$, $P < 0.001$). Fourth, Fig. 10*E* shows that the decrease in ROC area was significantly correlated with changes in the variance of visually driven activity. We measured this by computing the coefficient of variation of the visually driven responses on a trial-by-trial basis (i.e., the standard deviation divided by the mean activity), and the correlation between this measure and the change in ROC area was statistically significant ($r = -0.60$; $P < 0.001$). Interestingly, we found no relationship between the changes in ROC area and the analogous measure of variance in spontaneous activity ($r = +0.17$, $P > 0.1$; not illustrated). As a final link between ACPD effects on response mode and ROC area, Fig. 10*F* shows that, for the 47 cells showing at least some burst firing, decreases caused by ACPD application in burst index were significantly correlated with increases in the coefficient of variation in visually driven activity ($r = -0.61$; $P < 0.001$).

DISCUSSION

Our in vivo results indicate that activation of mGluRs on geniculate cells by the agonist ACPD causes these cells to respond to visual stimulation more in tonic mode and less in burst mode. This is an extension of prior in vitro observations, which demonstrated that activation of these receptors produces a slow, long-lasting depolarization, which inactivates the Ca^{2+} conductance underlying the low-threshold spike and thereby converts cells from the burst mode of responding to tonic (McCormick and Von Krosigk 1992). The available evidence indicates that certain mGluRs on relay cells are activated by corticogeniculate but not retinogeniculate axons (McCormick and Von Krosigk 1992), and thus our pharmacological activation of these receptors offers some insights into a possible role for the corticogeniculate pathway.

Specificity and route of ACPD effects

Because many of our observations are based on the effects on visual responses of applying ACPD, an agonist that activates mGluRs, it is worth considering the specificity and route of these effects. We have provided evidence that the result of ACPD application cannot be explained by activation of iGluRs, and that it appears to be mediated through mGluRs coupled to PI hydrolysis. Application of the specific NMDA antagonist APV did not antagonize the ACPD-mediated responses (Fig. 5). Likewise, application of mGluR antagonists failed to diminish responses generated by stimulation of AMPA receptors (Fig. 6). DHPG, an mGluR agonist that appears selective to PI-linked mGluRs (Schoepp et al. 1994), produced effects similar to those of the less specific agonist ACPD (Fig. 2). In addition, the antagonists used in this study, 4C3HPG and 4CPG, are also agonists to mGluRs negatively linked to the cAMP cascade, and neither had significant inhibitory or excitatory effects on its own. Furthermore, 4CPG seems to be ineffective as an antagonist to glutamate-stimulated inositol phosphate production mediated by splice variants of mGluR5, but both 4CPG and 4C3HPG are full competitive antagonists at mGluR1α, a

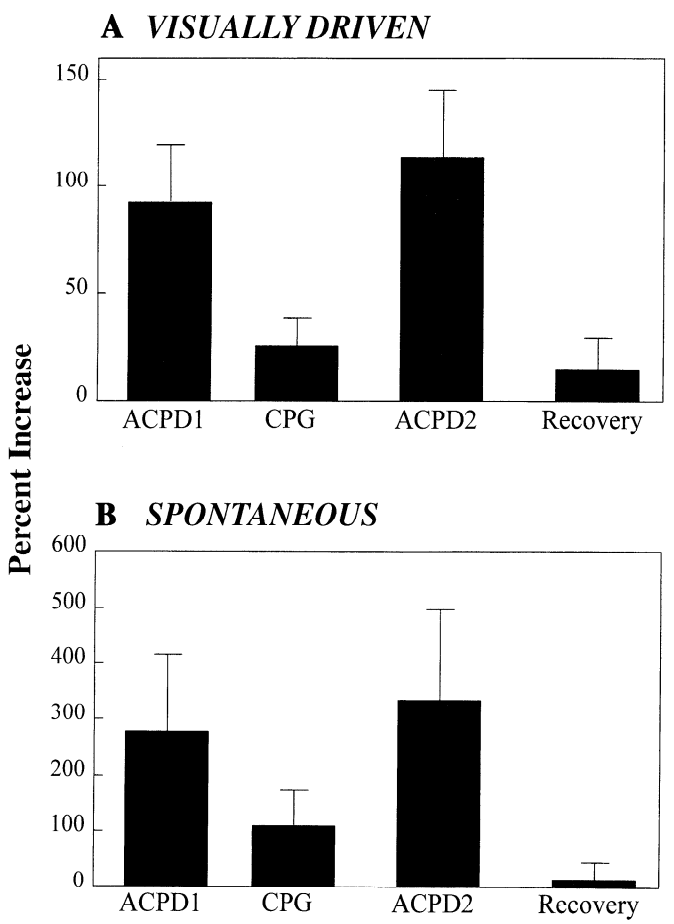

FIG. 8. Effects of phenylglycine antagonists [either 4CPG or s-4-carboxy-3-hydroxyphenylglycine (4C3HPG) for a given cell; data pooled across cells] on ACPD-elicited changes in responsiveness. The % changes in response levels are shown with the use of the same conventions as in Fig. 7, *bottom*. Bars in the histogram reflect a timed sequence from *left* to *right*: 1st the effects of ACPD application are shown (ACPD1), then the effects of adding phenylglycine antagonists (CPG), then the effects after terminating CPG application but sustaining the ACPD application (ACPD2), and finally the recovery after termination of all agonists and antagonists (Recovery). *A*: spontaneous activity. *B*: visually driven activity.

splice variant of mGluR1 (Joly et al. 1995). Because both drugs antagonized the effects of ACPD in the current study, we are led to conclude that our ACPD-mediated effects are through activation of mGluR1α, or a closely related mGluR. Although these related receptors share a link to PI hydrolysis, they may also be coupled to different second-messenger pathways (Conn et al. 1994), and our data do not address the specific intracellular route of these excitatory effects.

These physiological and pharmacological data are consistent with in vitro data showing that ACPD application depolarizes geniculate cells (McCormick and Von Krosigk 1992; Zhou et al. 1994). Because the effects reported here are antagonized by 4CPG, an antagonist to mGluR1 (Joly et al. 1995), these data are also in agreement with our preliminary anatomic observations showing that mGluR1α is present on geniculate relay cell dendrites postsynaptic to contacts from cortical terminals (Godwin et al. 1995). Also, our finding that 4CPG and 4C3HPG, both of which act as agonists to group II mGluRs, have no independent effect on geniculate cells is consistent with our failure to locate mGluR2 or mGluR3 in geniculate relay cells (Van Horn et al. 1995). Previous anatomic studies failed to detect messenger RNA for mGluR2 or mGluR3 in the rat lateral geniculate nucleus (Ohishi et al. 1993a,b). The role of other cAMP-coupled mGluRs (mGluR4 and mGluR7) in the lateral geniculate nucleus is left open, but results in rat ventrobasal thalamus indicate a possible disinhibitory role at inhibitory terminals originating from the thalamic reticular nucleus for some of these (Salt and Eaton 1995).

Possible ACPD effects on interneurons

For technical reasons, we were unable to unambiguously identify recorded geniculate neurons as relay cells or interneurons. That is, we did not employ techniques involving antidromic activation to identify relay cells, and other differences reported are very subtle (but see below). We can assume that most of the cells in our sample are relay cells, and thus the main conclusions certainly relate to these cells. Two other points are worth mentioning.

First, we note that regardless of how interneurons may change their firing patterns in response to ACPD application, this may have little effect on the synaptic release of γ-aminobutyric acid (GABA) by the interneuron. This is because of an unusual feature unique to these cells within the lateral geniculate nucleus: although they have a conventional axonal output that would be affected by firing rate, most of their synaptic output emanates from terminals located in the distal dendritic arbor (Hamos et al. 1985; Ralston 1971). Cable modeling suggests that these dendritic terminals are electrotonically distant from the soma (Bloomfield and Sherman 1989) and thus may not be much affected by firing rate. Instead, they innervate relay cells in complex synaptic zones in which they interact locally with other inputs, mostly retinal, to the same relay cell (Hamos et al. 1985; Ralston 1971). Thus the problem of determining effects of ACPD on interneurons is that we cannot be certain from conventional recording of action potentials near the soma that this tells us much about the postsynaptic effects these cells have via their dendritic outputs (Bloomfield and Sherman 1989).

In our sample of recorded cells were two X cells that behaved like interneurons (Pape and McCormick 1995; Pape et al. 1994): these cells did not show burst firing, and burst firing is rare in interneurons; also, their action potential durations were short, which is another feature of interneurons. Thus we suspect, but cannot prove, that these cells are interneurons. Interestingly, these two cells stand out in the sense that neither was affected by ACPD application in terms of the parameters we measured. Furthermore, although we did not observe significant effects with these cells, we observed significant ACPD effects on cells within the same electrode penetration, both above and below the recorded position of these cells, making it less likely that the lack of ACPD effects shown by these cells was due to failure of the iontophoretic electrode. These conclusions are consistent with the in vitro evidence of Pape and McCormick (1995) showing no effect of ACPD on identified interneurons in slices, and with our own anatomic data showing no evidence for the presence of mGluR1s in interneurons.

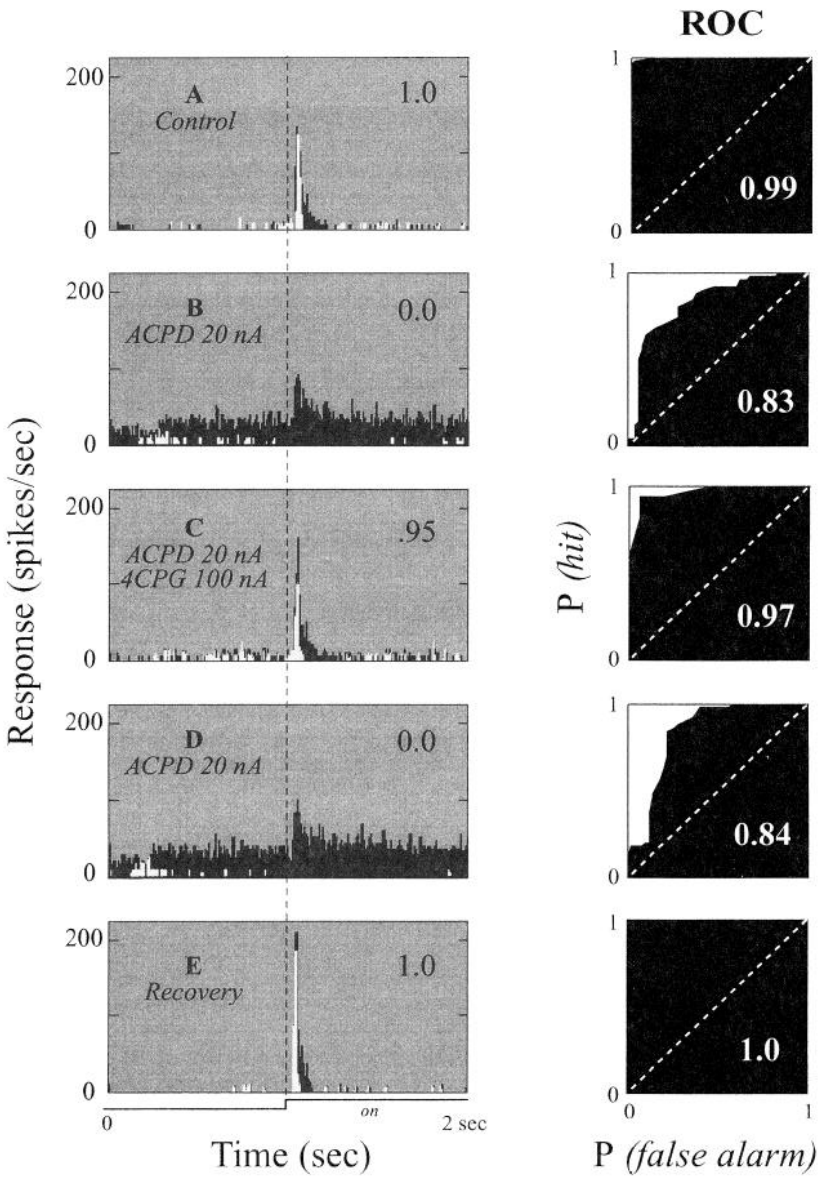

FIG. 9. Effects of ACPD application on response mode and of signal detectability on an on-center Y cell. The histograms at *left* follow the conventions of Fig. 2. *Right*: corresponding receiver operating characteristic (ROC) curves; the area under each curve is in black with the line of slope 1 and actual area under the curve indicated in white. *A*: response of cell during predrug control, showing extensive bursting in response to the flashed spot and large ROC area. *B*: response during application of ACPD, which eliminated bursting and reduced the ROC area. *C*: response during antagonism of ACPD by 4CPG, which restores most of bursting and raises ROC area. *D*: response to continued application of ACPD after removal of 4CPG, which restores responsiveness and ROC area seen in *B*. *E*: recovery after cessation of ACPD administration.

Control response mode by mGluR activation

In principle, any depolarizing input can inactivate the conductance underlying the low-threshold spike and thus promote tonic firing. Thus we cannot rule out the possibility that activation of iGluRs, such as AMPA and NMDA receptors from either retinal or cortical input, may powerfully control response mode along with activation of mGluRs from cortical input. However, there are reasons to conclude that the fast synaptic activation resulting from iGluR activation may not be suitable for such inactivation of the low-threshold spike. This is because synaptic activation of iGluRs produces an EPSP based on an increased Na^+/Ca^{2+} conductance that lasts only a few milliseconds. Although in principle this might inactivate the low-threshold spike for a very brief period, it may not provide for inactivation that lasts on the order of many seconds, as is seen with mGluR activation (McCormick and von Krosigk 1992).

If synaptic activation of iGluRs from retinal or cortical input were sufficiently sustained, this is unlikely to lead to prolonged depolarization, because the opening of the Na^+/Ca^{2+} conductance for more than a few milliseconds would cause a condition of depolarization block and possibly eventual neuronal damage (Greenamyre and Porter 1994; Lynch and Dawson 1994; McCulloch 1994; Meldrum 1994). Indeed, this phenomenon is thought to be the basis for NMDA-receptor-mediated neuronal ischemia (Greenamyre and Porter 1994; Lynch and Dawson 1994; McCulloch 1994; Meldrum 1994). Although we did observe a decrease in burst firing in Figs. 5 and 6 in response to continuous iontophoretic application of iGluRs, this is under special conditions that may be difficult to achieve with more natural synaptic activation. To obtain these records, an iontophoretic current was used that yielded a controllable increase in the neuronal discharge of the cell, but did not result in depolarization block. We found that only a narrow range of iontophoretic currents worked in this manner for activation of iGluRs.

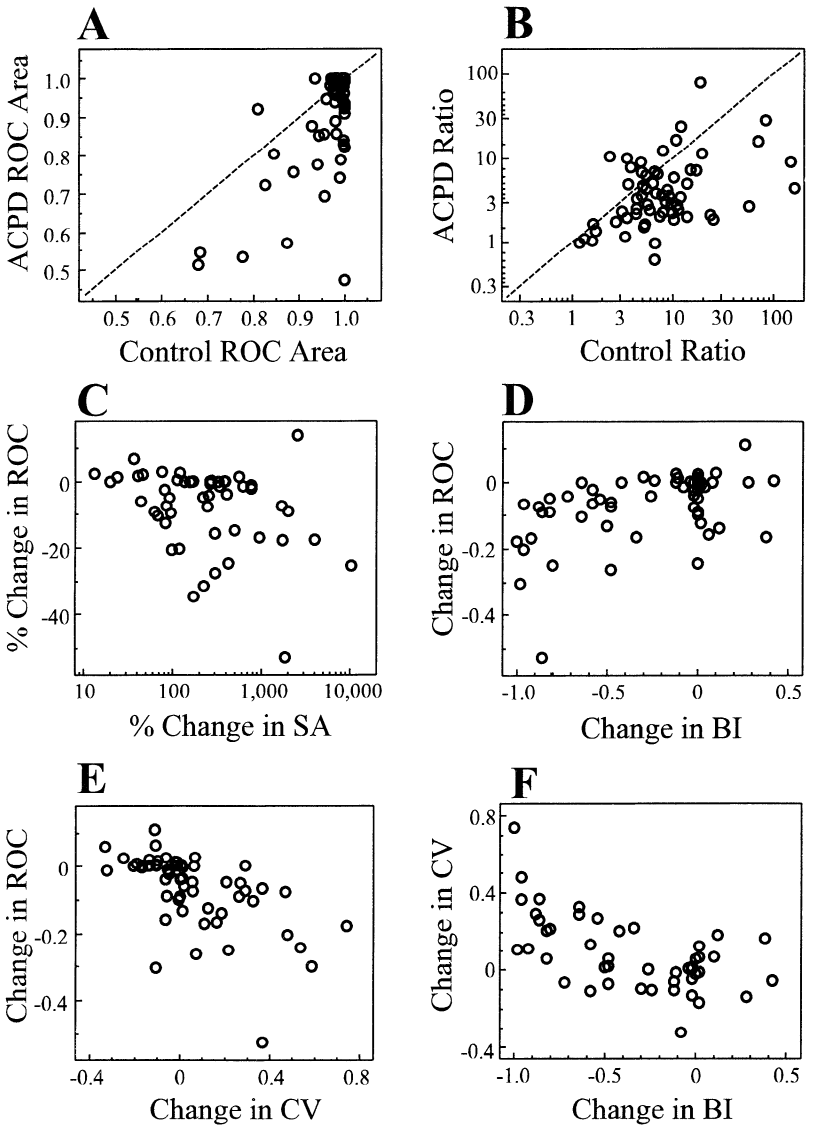

FIG. 10. Scatter plots showing various relationships among effects of ACPD application and responses for geniculate neurons. *A*: effect of ACPD on ROC area. The ROC areas before ACPD are plotted on the abscissa, and those during ACPD delivery are plotted on the ordinate. The line of slope 1 is indicated. ACPD lowers ROC areas for most cells. *B*: effect of ACPD on the ratio of visually driven to spontaneous activity. The ratios before ACPD are plotted on the abscissa, and those during ACPD delivery are plotted on the ordinate. The line of slope 1 is indicated. ACPD lowers these ratios for most cells. *C*: relationship between changes in burst index (abscissa) with changes in ROC area (ordinate). *D*: relationship between changes in burst index (abscissa) with changes in ROC area (ordinate). *E*: relationship between changes in coefficient of variation in the visually driven response (abscissa) with changes in ROC area (ordinate). *F*: relationship between changes in burst index (abscissa) with changes in coefficient of variation in the visually driven response (ordinate).

This is in contrast to mGluR activation, the result of which provided consistent effects on response mode over a wide range of iontophoretic currents. Synaptic activation of these receptors causes a very slow EPSP that lasts for several seconds. This is precisely what is needed to mediate the kind of dramatic transition from burst to tonic mode as observed in our study. Furthermore, the EPSP results from blocking an ongoing K^+ "leak" conductance, which limits the amplitude of the EPSP to ~10 mV. This is sufficient to inactivate the low-threshold spike, but does not cause the uncontrolled firing that would be expected with with massive iGluR activation. Thus, although we cannot rule out a role for iGluR in controlling response mode, this does not affect our main conclusion that the mGluRs indeed have a quite prominent role in controlling response mode.

Insights into function of the corticogeniculate pathway

The single largest input to the lateral geniculate nucleus derives from visual cortex, yet the function of the corticogeniculate pathway has remained elusive (reviewed in Koch 1987; Sherman 1993; Sherman and Koch 1986, 1990). Past studies have been somewhat confusing, some suggesting that the pathway facilitates relay cell firing, whereas others suggest the opposite (Baker and Malpeli 1977; Geisert et al. 1981; Kalil and Chase 1970; McClurkin and Marrocco 1984; Richard et al. 1975). Schmielau and Singer (1977) have proposed that corticogeniculate input is important to binocular functions, such as stereopsis. More recent studies have suggested that the pathway affects temporal properties of relay cell discharges (McClurkin et al. 1994) or establishes correlated firing among nearby relay cells with similar receptive field properties (Sillito et al. 1994). Despite these several hypotheses, we cannot yet assign any functions that would require the great size of the pathway, and its function remains one of the most important enigmas of thalamocortical relationships.

One interpretation of the data presented here is that it offers another means of determining the effects on the geniculate relay of activating the corticogeniculate input. This is

because ACPD serves as an agonist of mGluRs on relay cells, and the available evidence indicates that cortical axons are the main if not only glutamatergic input that can directly affect these receptors (McCormick and Von Krosigk 1992; Zhou et al. 1994). Thus application of ACPD would partly mimic activation of the corticogeniculate input. One important proviso to this interpretation is the evidence that corticogeniculate axons (as well as retinogeniculate axons) would also activate iGluRs. With our technique of locally applying agonists and antagonists to the geniculate neuron under investigation, we could not pharmacologically mimic full activation of corticogeniculate axons, which would require activation of both mGluRs and iGluRs, without also activating iGluRs associated with retinal inputs. However, activation of mGluRs, because they lead to prolonged depolarization (McCormick and Von Krosigk 1992), seems ideally suited to switching firing from burst to tonic, and the additional activation of iGluRs would provide further depolarization of a more temporally discrete nature. It is also plausible that mGluR activation and subsequent prolonged membrane depolarization affects synaptic transmission via iGluRs. In particular, NMDA receptors could be greatly facilitated by conjoint activation of mGluRs, because this would tend to relieve any hyperpolarization block of synaptic transmission dependent on NMDA receptors.

CONSEQUENCES OF EFFECTS ON RESPONSE MODE. It is now well established that both tonic and burst firing modes represent effective relay states for geniculate relay cells, because in both relay modes these cells respond vigorously to visual stimulation (present study; see also Guido et al. 1992, 1995; Lu et al. 1992, 1993; Mukherjee and Kaplan 1995). This basic observation of visual responsiveness in both modes has recently been extended to the awake, behaving cat (Guido and Weyand 1995), and it is thus not a peculiar artifact of the sort of anesthetized preparation used in our experiments. Several studies have begun to document the significance of these different response modes for the relay of visual information, and three such differences so far have been emphasized: tonic mode provides a more linear faithful relay (Guido et al. 1992; Mukherjee and Kaplan 1995); burst mode provides a relay better suited to signal detection (present paper; see also Guido et al. 1995); and the different modes affect the temporal tuning of relay cells, with the result that tonic firing acts more as a low-pass filter (Mukherjee and Kaplan 1995).

These different response patterns have led so far to two different suggestions for these different firing modes of relay cells. The first is based on better detectability but more nonlinear distortion in burst mode (Guido et al. 1992, 1995; Mukherjee and Kaplan 1995). It suggests that burst mode would be used when visual target detection was more important, so that the sudden presence of a potentially interesting or threatening object could be noted for further analysis. This could happen any time the receptive field of a geniculate relay cell in question was not involved in accurate analysis of a stimulus under study, such as occurs when a stimulus is being analyzed in another part of the visual field, during saccadic eye movements requiring reacquisition of a target, during visual search, when another sensory modality (e.g., hearing) is preferentially used, or during general inattentiveness or drowsiness. Burst mode would be useful under these circumstances to signal the presence of a new stimulus, but the nonlinearity of visual responses seen during this mode would make it less suitable to accurately analyze the stimulus. For this, tonic mode would be better (Guido et al. 1995), because the less nonlinear distortion means that the signal relayed to cortex is a more faithful representation of the incoming signal from retina. The second hypothesis, which is based on the different temporal tuning of the two response modes, suggests that these firing modes can act as a "tunable temporal filter" for the geniculate relay (Mukherjee and Kaplan 1995).

It is important to note, however, that these two notions are not contradictory and can be regarded as complementary. If a geniculate cell is in tonic mode to promote detailed and accurate stimulus analysis, it would have to be broadly responsive to temporal frequencies that would be present during fixation. On the other hand, if the cell is in burst mode to promote detection of changes in the visual scene, sensitivity to temporal frequencies in transients would be more important to signal these changes, and filtering out the lower temporal frequencies would keep the cell relatively unresponsive to unchanging features of the scene.

Whatever the detailed effects of changing response mode between tonic and burst, it seems clear that these modes can strongly affect the nature of the information relayed to cortex. Our evidence, albeit indirect, that corticogeniculate axons can have a powerful influence on response mode of the geniculate relay suggests that this feedback pathway can strongly influence the nature of the visual information provided to cortex. A number of previous studies have led to a variety of different hypotheses for the role of the corticogeniculate pathway (Baker and Malpeli 1977; Geisert et al. 1981; Kalil and Chase 1970; McClurkin and Marrocco 1984; McClurkin et al. 1994; Richard et al. 1975; Schmielau and Singer 1977; Sillito et al. 1994). Given the size of the corticogeniculate pathway, it seems plausible that it subserves multiple functions, and evidence does exist for heterogeneity within this pathway (Katz 1987; Tsumoto and Suda 1980). The idea presented here that the corticogeniculate pathway controls response mode is thus meant to represent only a partial role for this pathway.

Comparison of cortical versus brain stem inputs to the lateral geniculate nucleus

ACPD VERSUS BRAIN STEM ACTIVATION. Electrical activation of the brain stem inputs to the lateral geniculate nucleus in the cat provides a robust means of converting bursting geniculate cells to the tonic firing mode (Lu et al. 1993). This is at least superficially similar to the effects of ACPD application reported here and raises the possibility that the underlying mechanisms are similar. In fact, the available evidence suggests that many of the receptors activated by cortical and brain stem inputs converge onto the same set of transmembrane conductances. These transmitters include norepinephrine and acetylcholine, and in vitro studies point to a similar reduction of a K^+ leak conductance by activation of α_1 adrenoreceptors and by muscarinic cholinergic receptors (McCormick 1992). The in vitro evidence to date supports a similar control of this leak conductance by activation

of mGluRs (McCormick and Von Krosigk 1992; Zhou et al. 1994). In this context, it is not surprising that many of the effects reported here reflect response changes that have also been associated with brain stem activation (Lu et al. 1993).

DIFFERENT ROLES FOR CORTICAL VERSUS BRAIN STEM INPUTS. Even if cortical and brain stem inputs control common final conductances and have a similar effect on response mode, this is not to suggest that the two sources of input are organized to subserve the same function. One of the key features of organization of the corticogeniculate projection is its precise retinotopic order (Updyke 1975, 1977). A physiological concomitant of this was provided by Tsumoto et al. (1978), who studied the effects on visual responses of geniculate cells of local stimulation of cortical layer VI with glutamate. The effects were excitatory if the receptive fields of the geniculate cell and those of cortical cells within the region of the glutamate injection were aligned within ~2° of visual angle, and inhibitory if misaligned further. The inhibitory effects may reflect cortical activation of local inhibitory, GABAergic neurons (e.g., interneurons or cells of the thalamic reticular nucleus). From our present study, we would predict that the local excitation would be accompanied by activation of mGluRs and would tend to keep the relay in tonic mode for accurate analysis. The surrounding inhibition and, presumably, hyperpolarization of geniculate cells mapping areas outside of that represented by the receptive fields of the corticogeniculate axons would tend to promote burst responses in these geniculate cells, because both $GABA_A$- and $GABA_B$-receptor-mediated inhibition can contribute to burst firing through deinactivation of the current underlying the low-threshold spike (Deschênes et al. 1984; Soltész and Crunelli 1992). Thus the feedback from cortex may be capable of establishing tonic firing focally among groups of geniculate relay cells, and may simultaneously promote burst firing in surrounding geniculate cells to enhance vigilance for the sudden appearance of any novel stimuli. This in effect would create a sort of "spotlight" of focal attention for accurate analysis, in some ways analogous to Crick's (1984) "searchlight" hypothesis, and surround this with a zone in which new or changing stimuli can be detected with great sensitivity. The surround might be useful in tracking a stimulus in motion or to signal other parts of a large target being analyzed.

In contrast to this, the organization of the brain stem projection to the lateral geniculate nucleus seems much more diffuse (Uhlrich et al. 1988) and may thus influence the geniculate relay in a less discrete fashion. It is also quite heterogeneous, comprising pathways from different sources and employing different transmitters (for a review and more detailed description, see Sherman and Koch 1990). Functions ascribed to the various brain stem inputs range from general arousal requirements to more specific roles related to eye movements, among many others (Lal and Friedlander 1989; Sherman and Koch 1986, 1990; Steriade and McCarley 1990). In many of these cases, control of response mode may be a key result of brain stem input. Thus, although both brain stem and cortical inputs to geniculate neurons have similar effects on response mode and may even make use of similar cellular mechanisms to do so, the role in vision served by these different inputs is probably quite different, with cortical inputs controlling response mode much more selectively and focally than do those from brain stem.

This work was supported by a grant from the National Eye Institute (NEI) (EY-03038). D. W. Godwin was supported through National Institute of Neurological Disorders and Stroke Grant F32-NS-09163 and J. W. Vaughan by NEI Grant F32-EY-06340.

Present address of D. W. Godwin and J. W. Vaughan: Dept. of Neurobiology and Anatomy, Bowman Gray School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157-1023.

Address reprint requests to S. M. Sherman.

Received 27 October 1995; accepted in final form 30 April 1996.

REFERENCES

BAKER, F. H. AND MALPELI, J. G. Effects of cryogenic blockade of visual cortex on the responses of lateral geniculate neurons in the monkey. *Exp. Brain Res.* 29: 433–444, 1977.

BIRSE, E. F., EATON, S. A., JANE, D. E., JONES, P. L., PORTER, R. H., POOK, P. C., SUNTER, D. C., UDVARHELYI, P. M., WHARTON, B., AND ROBERTS, P. J. Phenylglycine derivatives as new pharmacological tools for investigating the role of metabotropic glutamate receptors in the central nervous system. *Neuroscience* 52: 481–488, 1993.

LOOMFIELD, S. A. AND SHERMAN, S. M. Dendritic current flow in relay cells and interneurons of the cat's lateral geniculate nucleus. *Proc. Natl. Acad. Sci. USA* 86: 3911–3914, 1989.

COLWELL, C. S. AND LEVINE, M. S. Metabotropic glutamate receptors modulate *N*-methyl-D-aspartate receptor function in neostriatal neurons. *Neuroscience* 61: 497–507, 1994.

CONN, P. J., BOSS, V., AND CHUNG, D. S. Second messenger systems coupled to metabotropic glutamate receptors. In: *The Metabotropic Glutamate Receptors,* edited by P. J. Conn and J. Patel. Totowa, NJ: Humana, 1994, p. 59–98.

CRICK, F. Function of the thalamic reticular complex: the searchlight hypothesis. *Proc. Natl. Acad. Sci. USA* 81: 4586–4590, 1984.

DESCHÊNES, M., PARADIS, M., ROY, J. P., AND STERIADE, M. Electrophysiology of neurons of lateral thalamic nuclei in cat: resting properties and burst discharges. *J. Neurophysiol.* 51: 1196–1219, 1984.

DUVOISIN, R. M., ZHANG, C., AND RAMONELL, K. A novel metabotropic receptor expressed in the retina and olfactory bulb. *J. Neurosci.* 15: 3075–3083, 1995.

EYSEL, U. T., PAPE, H.-C., AND VAN SCHAYCK, R. Excitatory and differential disinhibitory actions of acetylcholine in the lateral geniculate nucleus of the cat. *J. Physiol. Lond.* 370: 233–254, 1986.

FRANCESCONI, W., MÜLLER, C. M., AND SINGER, W. Cholinergic mechanisms in the reticular control of transmission in the cat lateral geniculate nucleus. *J. Neurophysiol.* 59: 1690–1718, 1988.

GEISERT, E. E., LANGSETMO, A., AND SPEAR, P. D. Influence of the corticogeniculate pathway on reponse properties of cat lateral geniculate neurons. *Brain Res.* 208: 409–415, 1981.

GODWIN, D. W. A tungsten-in-glass iontophoresis assembly for studying input-output relationships in central neurons. *J. Neurosci. Methods* 49: 211–223, 1993.

GODWIN, D. W., VAN HORN, S. C., GÜNLÜK, A. E., SESMA, M. A., ROMANO, C., AND SHERMAN, S. M. Localization of two metabotropic glutamate receptors (mGluR1α and mGluR5) in cat LGN. *Soc. Neurosci. Abstr.* 21: 658, 1995.

GODWIN, D. W., VAUGHAN, J. W., AND SHERMAN, S. M. Metabotropic glutamate receptors switch firing mode of cat LGN cells in vivo from burst to tonic. *Soc. Neurosci. Abstr.* 20: 7, 1994.

GREENAMYRE, J. T. AND PORTER, R. H. Anatomy and physiology of glutamate in the CNS (Review). *Neurology* 44: 7–13, 1994.

GRIEVE, K. L. AND SILLITO, A. M. Differential properties of cells in the feline primary visual cortex providing the corticofugal feedback to the lateral geniculate nucleus and visual claustrum. *J. Neurosci.* 15: 4868–4874, 1995.

GUIDO, W., LU, S.-M., AND SHERMAN, S. M. Relative contributions of burst and tonic responses to the receptive field properties of lateral geniculate neurons in the cat. *J. Neurophysiol.* 68: 2199–2211, 1992.

GUIDO, W., LU, S.-M., VAUGHAN, J. W., GODWIN, D. W., AND SHERMAN, S. M. Receiver operating characteristic (ROC) analysis of neurons in the

cat's lateral geniculate nucleus during tonic and burst response mode. *Visual Neurosci.* 1995.

GUIDO, W. AND WEYAND, T. Burst responses in lateral geniculate neurons of the awake behaving cat. *J. Neurophysiol.* 74: 1782–1786, 1995.

HAMOS, J. E., VAN HORN, S. C., RACZKOWSKI, D., UHLRICH, D. J., AND SHERMAN, S. M. Synaptic connectivity of a local circuit neurone in lateral geniculate nucleus of the cat. *Nature Lond.* 317: 618–621, 1985.

HAYASHI, Y., SEKIYAMA, N., NAKANISHI, S., JANE, D. E., SUNTER, D. C., BIRSE, E. F., UDVARHELYI, P. M., AND WATKINS, J. C. Analysis of agonist and antagonist activities of phenylglycine derivatives for different cloned metabotropic glutamate receptor subtypes. *J. Neurosci.* 14: 3370–3377, 1994.

HOLDEFER, R. N., NORTON, T. T., AND GODWIN, D. W. Effects of bicuculline on signal detectability in lateral geniculate nucleus relay cells. *Brain Res.* 488: 341–347, 1989.

JAHNSEN, H. AND LLINÁS, R. Electrophysiological properties of guinea-pig thalamic neurones: an in vitro study. *J. Physiol. Lond.* 349: 205–226, 1984a.

JAHNSEN, H. AND LLINÁS, R. Ionic basis for the electroresponsiveness and oscillatory properties of guinea-pig thalamic neurones in vitro. *J. Physiol. Lond.* 349: 227–247, 1984b.

JOLY, C., GOMEZA, J., BRABET, I., CURRY, K., BOCKAERT, J., AND PIN, J. P. Molecular, functional, and pharmacological characterization of the metabotropic glutamate receptor type 5 splice variants: comparison with mGluR1. *J. Neurosci.* 15: 3970–3981, 1995.

KALIL, R. E. AND CHASE, R. Corticofugal influence on activity of lateral geniculate neurons in the cat. *J. Neurophysiol.* 33: 459–474, 1970.

KATZ, L. C. Local circuitry of identified projection neurons in cat visual cortex brain slices. *J. Neurosci.* 7: 1223–1249, 1987.

KEMP, J. A. AND SILLITO, A. M. The nature of the excitatory transmitter mediating X and Y cell inputs to the cat dorsal lateral geniculate nucleus. *J. Physiol. Lond.* 323: 377–391, 1982.

KOCH, C. The action of the corticofugal pathway on sensory thalamic nuclei: a hypothesis. *Neuroscience* 23: 399–406, 1987.

KWON, Y. H., ESGUERRA, M., AND SUR, M. NMDA and non-NMDA receptors mediate visual responses of neurons in the cat's lateral geniculate nucleus. *J. Neurophysiol.* 66: 414–428, 1991.

LAL, R. AND FRIEDLANDER, M. J. Gating of retinal transmission by afferent eye position and movement signals. *Science Wash. DC* 243: 93–96, 1989.

LIVINGSTONE, M. S. AND HUBEL, D. H. Effects of sleep and arousal on the processing of visual information in the cat. *Nature Lond.* 291: 554–561, 1981.

LO, F.-S., LU, S.-M., AND SHERMAN, S. M. Intracellular and extracellular in vivo recording of different response modes for relay cells of the cat's lateral geniculate nucleus. *Exp. Brain Res.* 83: 317–328, 1991.

LU, S.-M., GUIDO, W., AND SHERMAN, S. M. Effects of membrane voltage on receptive field properties of lateral geniculate neurons in the cat: contributions of the low threshold Ca^{++} conductance. *J. Neurophysiol.* 68: 2185–2198, 1992.

LU, S.-M., GUIDO, W., AND SHERMAN, S. M. The brainstem parabrachial region controls mode of response to visual stimulation of neurons in the cat's lateral geniculate nucleus. *Visual Neurosci.* 10: 631 642, 1993.

LYNCH, D. R. AND DAWSON, T. M. Secondary mechanisms in neuronal trauma (Review; see comments). *Curr. Opin. Neurol.* 7: 510–516, 1994.

MACMILLAN, N. A. AND CREELMAN, C. D. *Detection Theory: A User's Guide.* Cambridge, UK: Cambridge Univ. Press, 1991.

MAYER, M. L. AND WESTBROOK, G. L. The physiology of excitatory amino acids in the vertebrate central nervous system. *Prog. Neurobiol.* 28: 197–276, 1987.

MCCLURKIN, J. W. AND MARROCCO, R. T. Visual cortical input alters spatial tuning in monkey lateral geniculate nucleus cells. *J. Physiol. Lond.* 348: 135–152, 1984.

MCCLURKIN, J. W., OPTICAN, L. M., AND RICHMOND, B. J. Cortical feedback increases visual information transmitted by monkey parvocellular lateral geniculate nucleus neurons. *Visual Neurosci.* 11: 601–617, 1994.

MCCORMICK, D. A. Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. *Prog. Neurobiol.* 39: 337–388, 1992.

MCCORMICK, D. A. AND FEESER, H. R. Functional implications of burst firing and single spike activity in lateral geniculate relay neurons. *Neuroscience* 39: 103–113, 1990.

MCCORMICK, D. A. AND PRINCE, D. A. Actions of acetylcholine in the guinea-pig and cat medial and lateral geniculate nuclei, in vitro. *J. Physiol. Lond.* 392: 147–165, 1987.

MCCORMICK, D. A. AND VON KROSIGK, M. Corticothalamic activation modulates thalamic firing through glutamate "metabotropic" receptors. *Proc. Natl. Acad. Sci. USA* 89: 2774–2778, 1992.

MCCULLOCH, J. Glutamate receptor antagonists in cerebral ischaemia (Review). *J. Neural. Transm. Gen. Sect.* 43, *Suppl.*: 71–79, 1994.

MELDRUM, B. S. The role of glutamate in epilepsy and other CNS disorders (Review). *Neurology* 44: 14–23, 1994.

MONTERO, V. M. Quantitative immunogold evidence for enrichment of glutamate but not aspartate in synaptic terminals of retino-geniculate, geniculo-cortical, and cortico-geniculate axons in the cat. *Visual Neurosci.* 11: 675–681, 1994.

MUKHERJEE, P. AND KAPLAN, E. Dynamics of neurons in the cat lateral geniculate nucleus: in vivo electrophysiology and computational modeling. *J. Neurophysiol.* 74: 1222–1243, 1995.

NORTON, T. T. AND GODWIN, D. W. Inhibitory GABAergic control of visual signals at the lateral geniculate nucleus (Review). *Prog. Brain Res.* 90: 193–217, 1992.

OHISHI, H., SHIGEMOTO, R., NAKANISHI, S., AND MIZUNO, N. Distribution of the mRNA for a metabotropic glutamate receptor (mGluR3) in the rat brain: an in situ hybridization study. *J. Comp. Neurol.* 335: 252–266, 1993a.

OHISHI, H., SHIGEMOTO, R., NAKANISHI, S., AND MIZUNO, N. Distribution of the messenger RNA for a metabotropic glutamate receptor, mGluR2, in the central nervous system of the rat. *Neuroscience* 53: 1009–1018, 1993b.

PALMER, E., MONAGHAN, D. T., AND COTMAN, C. W. Trans-ACPD, a selective agonist of the phosphoinositide-coupled excitatory amino acid receptor. *Eur. J. Pharmacol.* 166: 585–587, 1989.

PAPE, H.-C., BUDDE, T., MAGER, R., AND KISVARÁDAY, Z. F. Prevention of Ca^{2+}-mediated action potentials in GABAergic local circuit neurones of rat thalamus by a transient K^+ current. *J. Physiol. Lond.* 478: 403–422, 1994.

PAPE, H.-C. AND MCCORMICK, D. A. Electrophysiological and pharmacological properties of interneurons in the cat dorsal lateral geniculate nucleus. *Neuroscience* 68: 1105–1125, 1995.

PETTIGREW, J. D., COOPER, M. L., AND BLASDEL, G. G. Improved use of tapetal reflection for eye-position monitoring. *Invest. Ophthalmol. Visual Sci.* 18: 490–495, 1979.

RALSTON, H. J., III. Evidence for presynaptic dendrites and a proposal for their mechanism of action. *Nature Lond.* 230: 585–587, 1971.

RICHARD, D., GIOANNI, Y., KITSIKIS, A., AND BUSER, P. A study of geniculate unit activity during cryogenic blockade of the primary visual cortex in the cat. *Exp. Brain Res.* 22: 235–242, 1975.

SALT, T. E. AND EATON, S. A. The function of metabotropic excitatory amino acid receptors in synaptic transmission in the thalamus: studies with novel phenylglycine antagonists. *Neurochem. Int.* 24: 451–458, 1994.

SALT, T. E. AND EATON, S. A. Distinct presynaptic metabotropic receptors for L-AP4 and CCG1 on GABAergic terminals: pharmacological evidence using novel α-methyl derivative mGluR antagonists, MAP4 and MCCG, in the rat thalamus in vivo. *Neuroscience* 65: 5–13, 1995.

SCHARFMAN, H. E., LU, S.-M., GUIDO, W., ADAMS, P. R., AND SHERMAN, S. M. *N*-methyl-D-aspartate (NMDA) receptors contribute to excitatory postsynaptic potentials of cat lateral geniculate neurons recorded in thalamic slices. *Proc. Natl. Acad. Sci. USA* 87: 4548–4552, 1990.

SCHMIELAU, F. AND SINGER, W. The role of visual cortex for binocular interactions in the cat lateral geniculate nucleus. *Brain Res.* 120: 354–361, 1977.

SCHOEPP, D. D., GOLDSWORTHY, J., JOHNSON, B. G., SALHOFF, C. R., AND BAKER, S. R. 3,5-dihydroxyphenylglycine is a highly selective agonist for phosphoinositide-linked metabotropic glutamate receptors in the rat hippocampus. *J. Neurochem.* 63: 769–772, 1994.

SHAPLEY, R. AND LENNIE, P. Spatial frequency analysis in the visual system. *Annu. Rev. Neurosci.* 8: 547–583, 1985.

SHERMAN, S. M. Functional organization of the W-, X-, and Y-cell pathways in the cat: a review and hypothesis. In: *Progress in Psychobiology and Physiological Psychology,* edited by J. M. Sprague and A. N. Epstein. Orlando, FL: Academic, 1985, vol. 11, p. 233–314.

SHERMAN, S. M. Dynamic gating of retinal transmission to the visual cortex by the lateral geniculate nucleus. In: *Thalamic Networks for Relay and Modulation,* edited by D. Minciacchi, M. Molinari, G. Macchi, and E. G. Jones. Oxford, UK: Pergamon, 1993, p. 61–79.

SHERMAN, S. M. Dual response modes in lateral geniculate neurons: mechanisms and functions. *Visual Neurosci.* 13: 205–213, 1996.

SHERMAN, S. M. AND KOCH, C. The control of retinogeniculate transmission in the mammalian lateral geniculate nucleus. *Exp. Brain Res.* 63: 1–20, 1986.

SHERMAN, S. M. AND KOCH, C. Thalamus. In: *The Synaptic Organization of the Brain* (3rd ed.), edited by G. M. Shepherd. New York: Oxford Univ. Press, 1990, p. 246–278.

SILLITO, A. M., JONES, H. E., GERSTEIN, G. L., AND WEST, D. C. Feature-linked synchronization of thalamic relay cell firing induced by feedback from the visual cortex. *Nature Lond.* 369: 479–482, 1994.

SILLITO, A. M., MURPHY, P. C., SALT, T. E., AND MOODY, C. I. Dependence of retinogeniculate transmission in cat on NMDA receptors. *J. Neurophysiol.* 63: 347–355, 1990.

SINGER, W. Control of thalamic transmission by corticofugal and ascending reticular pathways in the visual system. *Physiol. Rev.* 57: 386–420, 1977.

SOLTÉSZ, I. AND CRUNELLI, V. $GABA_A$, and pre- and post-synaptic $GABA_B$ receptor-mediated responses in the lateral geniculate nucleus. *Prog. Brain Res.* 90: 151–169, 1992.

STERIADE, M. AND LLINÁS, R. The functional states of the thalamus and the associated neuronal interplay. *Physiol. Rev.* 68: 649–742, 1988.

STERIADE, M. AND MCCARLEY, R. W. *Brainstem Control of Wakefulness and Sleep.* New York: Plenum, 1990.

STERIADE, M., MCCORMICK, D. A., AND SEJNOWSKI, T. J. Thalamocortical oscillations in the sleeping and aroused brain. *Science Wash. DC* 262: 679–685, 1993.

TSUMOTO, T., CREUTZFELDT, O. D., AND LEGENDY, C. R. Functional organization of the cortifugal system from visual cortex to lateral geniculate nucleus in the cat. *Exp. Brain Res.* 32: 345–364, 1978.

TSUMOTO, T. AND SUDA, K. Three groups of cortico-geniculate neurons and their distribution in binocular and monocular segments of cat striate cortex. *J. Comp. Neurol.* 193: 223–236, 1980.

UHLRICH, D. J., CUCCHIARO, J. B., AND SHERMAN, S. M. The projection of individual axons from the parabrachial region of the brainstem to the dorsal lateral geniculate nucleus in the cat. *J. Neurosci.* 8: 4565–4575, 1988.

UPDYKE, B. V. The patterns of projection of cortical areas 17, 18, and 19 onto the laminae of the dorsal lateral geniculate nucleus in the cat. *J. Comp. Neurol.* 163: 377–396, 1975.

UPDYKE, B. V. Topographic organization of the projections from cortical areas 17, 18, and 19 onto the thalamus, pretectum and superior colliculs in the cat. *J. Comp. Neurol.* 173: 81–122, 1977.

VAN HORN, S. C., GODWIN, D. W., GÜNLÜK, A. E., AND SHERMAN, S. M. Can glutamate be inhibitory in cat thalamic reticular nucleus (TRN)? *Soc. Neurosci. Abstr.* 21: 658, 1995.

WATKINS, J. AND COLLINGRIDGE, G. Phenylglycine derivatives as antagonists of metabotropic glutamate receptors (Review). *Trends Pharmacol. Sci.* 15: 333–342, 1994.

WILSON, J. R., BULLIER, J., AND NORTON, T. T. Signal-to noise comparisons for X and Y cells in the retina and lateral geniculate nucleus of the cat. *Exp. Brain Res.* 70: 399–405, 1988.

ZHOU, Q., GODWIN, D. W., BICKFORD, M. E., SHERMAN, S. M., AND ADAMS, P. R. Relay cells and local GABAergic cells contribute to responses mediated by metabotropic glutamate receptors in cat LGN. *Soc. Neurosci. Abstr.* 20: 133, 1994.