Visual responses in adult cat visual cortex depend on N-methyl-D-aspartate receptors

(excitatory synaptic transmission/excitatory amino acids/aminophosphonovalerate/kainate/quisqualate)

K. D. MILLER*†‡, B. CHAPMAN§, AND M. P. STRYKER*§

Department of *Physiology and §Neuroscience Graduate Program, University of California, San Francisco, CA 94143-0444; and †Department of Neurobiology, Stanford University School of Medicine, Stanford, CA 94305

ABSTRACT   We have investigated the role of the N-methyl-D-aspartate (NMDA) receptor, a subtype of glutamate receptor, in the responses of cells in adult cat visual cortex. After intracortical infusion of the NMDA receptor antagonist DL-2-amino-5-phosphonovalerate (DL-APV) for one day, iontophoretic responses to NMDA, to kainate, and to quisqualate revealed a receptor blockade specific to NMDA receptors and extending several millimeters from the cannula. In this region, neuronal responses to visual stimulation were profoundly suppressed, in a manner strongly correlated with the degree of NMDA receptor blockade. Neither NMDA receptor blockade nor activity suppression was caused by the inactive stereoisomer L-APV. Hence, we conclude that NMDA receptors make a major contribution to normal excitatory transmission in adult visual cortex.

Excitatory synaptic transmission in visual cortex depends on glutamate receptors. Kynurenate, a general blocker of these receptors, abolishes excitatory postsynaptic potentials (EPSPs) and responses to glutamate agonists in cultured cells (1) and slices (2) of visual cortex. An important issue for the understanding of cortical function is the contribution of each subtype of glutamate receptor to excitatory transmission.

Glutamate receptors are of two general types (3). One type, which appears to have multiple subtypes, is the kainate/quisqualate (KA/QUIS) receptor. Activation of this type of receptor leads to a conventional fast EPSP. The other type of glutamate receptor is the N-methyl-D-aspartate (NMDA) receptor. When it is activated, it causes a slow, long-lasting EPSP (4–11).

We have studied the role of the NMDA receptor in excitatory synaptic transmission in visual cortex. Previous reports (12, 13) have concluded that NMDA receptors contribute to excitatory transmission in the visual cortex of young kittens during the critical period for synaptic plasticity, but that they do not do so appreciably in adult cats. To study the role of NMDA receptors in cortical synaptic transmission, several conditions must be achieved. First, one needs to produce a blockade of NMDA receptors which is uniform at least over the full extent of an individual cell's synaptic input. Second, one must be able to assess the degree and the specificity of NMDA blockade at each cortical site studied. Then one may assess the effect of that blockade on spontaneous and visually driven activity.

To achieve a locally uniform blockade, we have chronically infused the cortex with the NMDA-receptor-blocker 2-amino-5-phosphonovalerate (APV). We found that APV infusion created a specific blockade of NMDA receptors over several millimeters of cortex. In this region, neuronal responses to visual stimulation were profoundly suppressed, in a manner strongly correlated with the degree of NMDA blockade. We interpret these results to suggest that visual

responses, in at least a critical subset of visual cortical cells, depend on a slow EPSP mediated by activation of NMDA receptors in response to high-frequency sensory input. An abstract of this work has appeared (14).

MATERIALS AND METHODS

In six adult cats a 33-gauge cannula (200 μm outer diameter) was implanted under aseptic conditions 2 mm below the cortical surface into the representation of the central visual fields of one hemisphere of primary visual cortex (Horsley–Clarke coordinates AP -1-0, LM 2). The cannula was attached to an osmotic minipump (Alza 2001) delivering 1 μl/hr of 50 mM (pH 7.2–7.6) DL-APV (four animals) or of the active stereoisomer, D-APV (two animals). Opposite hemispheres were either left untreated (three animals) or implanted with a cannula delivering saline (one animal) or the inactive stereoisomer, L-APV (two animals). APV infusions continued throughout the recording sessions. Five of these animals were used to study visually evoked and spontaneous cortical activity and responses to NMDA and KA. The sixth animal was used to study responses to NMDA and QUIS. In a seventh animal, one hemisphere was treated with L-APV and the opposite hemisphere was untreated. The control data include results only from untreated and saline-treated hemispheres.

One day after implantation, animals were prepared for physiological recording. Methods are as described previously (15), except that gallamine triethiodide rather than pancuronium bromide was used for neuromuscular blockade. Ketamine and similar anesthetics known to affect NMDA receptors were never used.

Physiological measurements were made with tungsten recording electrodes (16) glued to three-barreled glass electrodes. The glass electrodes had one barrel filled with KA or QUIS (20 mM, pH 7.2–7.6), one with NMDA (50 mM, pH 7.2–7.6), and one with saline.

Vertical microelectrode penetrations were made into primary visual cortex at various distances anterior to the APV cannula. Neural activity was studied at regular intervals of 200 or 300 μm. At each recording site, we assessed visually evoked and spontaneous neural discharge, the threshold to activation by iontophoretic application of NMDA, and the threshold to activation by iontophoretic application of KA or QUIS. The threshold measurements delineated the region of cortex in which NMDA receptors were specifically blocked.

We studied multiunit activity at regular intervals, rather than single isolated cells, to obtain a representative sample in a situation in which many sites had little or no spontaneous or visually driven activity. We summarized the multiunit activity at each site on a six-point scale: 0, neither sponta-

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Abbreviations: NMDA, N-methyl-D-aspartate; KA, kainate (kainic acid); QUIS, quisqualate; APV, 2-amino-5-phosphonovalerate; EPSP, excitatory postsynaptic potential.
‡To whom reprint requests should be sent at the * address.

neous nor visually driven activity of cortical neurons; 1, spontaneous cortical activity only, no visually driven activity; 2, unreliably driven visual responses; 3, weakly but reliably driven, sluggish visual responses; 4, reliable, vigorous visual responses by at least one cell; 5, strong multiunit visual responses. Visual responses were always assessed before drug thresholds were tested.

Drug thresholds were assessed as follows and as shown in Fig. 1. A spike discriminator was set to detect all spikes with amplitude above the noise level. For each drug, we collected three 4-sec samples of spontaneous activity or zero drug current (shown at the left of each panel in Fig. 1 *a–d*). Drug current was then increased by regular steps every 4 sec, until a peak response was passed or until the limits of our equipment—generally 1000 nA—were reached (some sites showed no response to NMDA). Step sizes ranged from 5 to 50 nA. Threshold was assessed as that current which first gave a response equal to twice the average spontaneous level of activity and at least two spikes per second. When no response was obtained, the threshold was assigned the largest current we could test. We allowed at least 3 min between assessment of KA or QUIS threshold and assessment of NMDA threshold, and we alternated, with each site, whether KA/QUIS or NMDA was the first tested. Equal holding currents of 5–10 nA were generally used on drug-containing barrels, balanced by opposite current on the saline barrel. In each animal, drug thresholds for each electrode were assessed first in control cortex. Periodic penetrations into untreated cortex were made throughout each experiment to ensure that electrode characteristics were unchanged.

RESULTS

After one day of APV infusion, a specific blockade of NMDA receptors was achieved. Typical responses to drug applications, and the method of assessment of drug thresholds, are illustrated in Fig. 1. In control cortex, multiunit responses to iontophoretic application of KA (*a*) and NMDA (*b*) were similar. In D- or DL-APV-treated cortex, responses to NMDA (*d, h–j*) were profoundly blocked except with very high iontophoretic currents, while responses to KA (*c*) remained vigorous and normal. Responses to QUIS (*e–g*) were entirely like those to KA.

Specificity of blockade is indicated by the lack of elevation of thresholds to activation by KA or QUIS even at the closest distances to the cannula. Fig. 2 illustrates results from all animals as a function of distance from the D- or DL-APV cannula. In the five animals in which responses to KA and NMDA were studied, blockade of NMDA receptors (*a*) was seen within 3–4 mm from the cannula, while responses to KA were unaffected even very close to the cannula (*b*). In the animal in which responses to QUIS and NMDA were studied, a blockade of NMDA receptors (*d*) again was seen close to the cannula, while responses to QUIS (*e*) were unaffected.

Specificity of the blockade is also demonstrated by examining the dependence of QUIS or KA thresholds on NMDA thresholds at each site (Fig. 3). There is no tendency for elevation of NMDA thresholds to be accompanied by an elevation of thresholds to QUIS (*a*) or KA (*b*).

Vigorous neuronal activity was lacking where NMDA thresholds were elevated. Activity was assessed systematically in the five animals in which drug responses to KA and NMDA were assessed. Blockade of activity closely paralleled blockade of NMDA receptors as a function of distance from the cannula (Fig. 2c). Activity was profoundly suppressed within 3–4 mm from the cannula, where NMDA thresholds were strongly elevated. Mild elevations of threshold to NMDA activation, and correspondingly mild depressions of visual responses, were seen from 4 to 7 mm from the cannula. Neural activity appeared equally suppressed in the animal in which QUIS was studied.
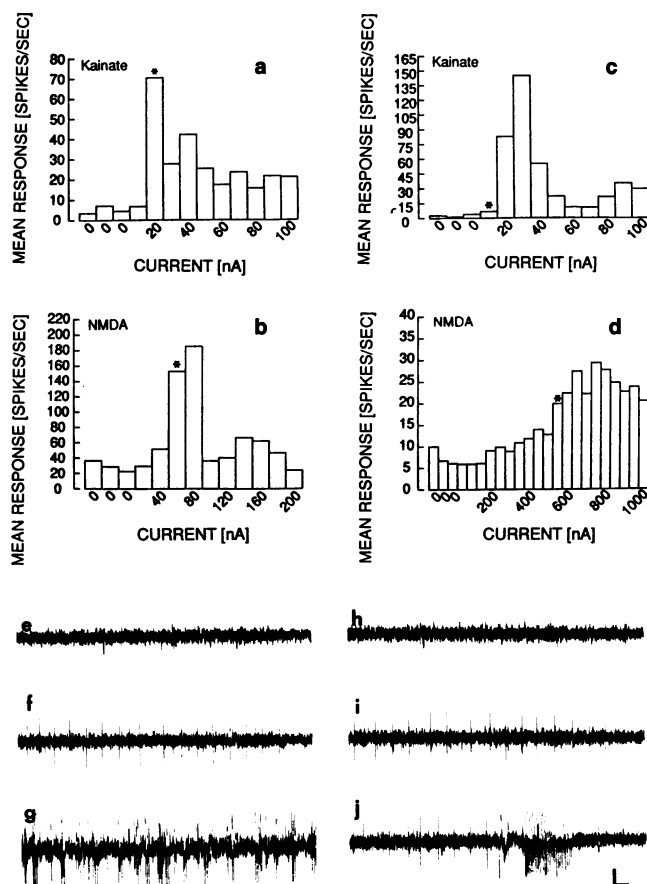

FIG. 1.   (*a–d*) Multiunit responses to drug applications. Bins with asterisks indicate threshold. Drug current was steadily increased every 4 sec after three 4-sec bins of zero current. Each bin represents response in one such 4-sec interval. (*a* and *b*) Drug responses at a typical unblocked site, 2.4 mm anterior to a cannula pumping the inactive stereoisomer L-APV. KA was stepped by 10 nA, NMDA by 20 nA. Threshold was 20 nA for KA, 60 nA for NMDA. Activity had been rated 5 at this site. (*c* and *d*) Typical drug responses where NMDA receptors were blocked, 1.04 mm anterior to D-APV cannula in same animal as in *a* and *b*. KA response normal and vigorous; KA threshold 10 nA. NMDA threshold assessed in 50-nA steps, because threshold had been found to be highly elevated. NMDA threshold response 550 nA. Activity had been rated 1 at this site. (*e–j*) Raw multiunit records where NMDA receptors were blocked, 1.2 mm anterior to DL-APV cannula in another animal. To left are responses to QUIS iontophoresis at 0 nA (*e*), 25 nA (*f*, threshold), and 65 nA (*g*, peak response). To right are responses to NMDA iontophoresis at 450 nA (*h*), 500 nA (*i*, threshold), and 1000 nA (*j*, peak response). At unblocked sites, NMDA records were indistinguishable from KA or QUIS records. Calibration bars correspond to 20 μV and 20 msec. The threshold and peak response currents were consistent and reproducible. After being excited by drugs, some cells in the population desensitize quickly; others require longer times or higher currents before desensitization. Hence, the shapes of the postpeak part of the histogram are extremely variable and without significance. In the blocked regions, the entire population may not be excited near the threshold of first response. In these regions, responses can be spread over a much broader range of currents as shown.

Activity suppression was strongly correlated with NMDA receptor blockade when data were analyzed site by site (Fig. 4). Sites that lacked vigorously driven visual responses (activity ratings 0–3) had strongly elevated NMDA thresholds (*a*) but normal KA thresholds (*b*). This correlation did not result from mechanical damage near the cannula tip, since it was present even when, as in Fig. 4, sites within 1 mm of the cannula were excluded from analysis. Sites with vigorous visual responses (activity ratings 4–5) had normal NMDA and KA thresholds. Conversely, at sites with sufficient elevation
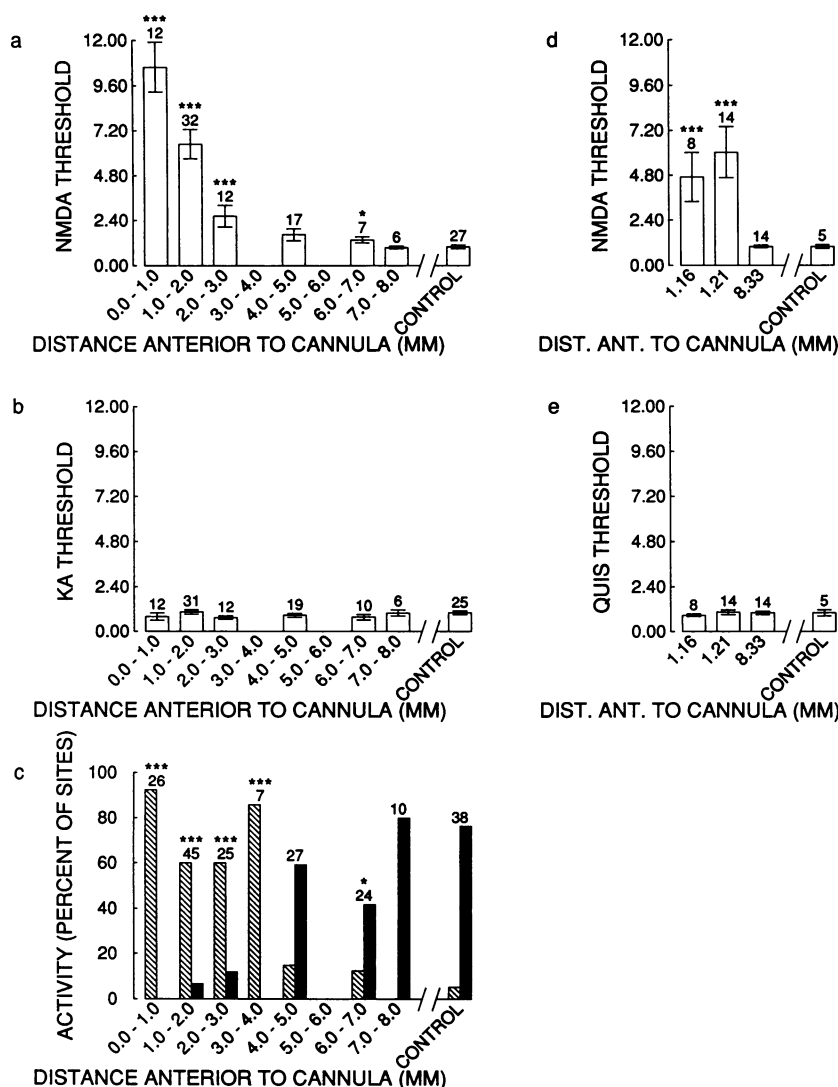
FIG. 2. Blockade of NMDA, compared to responses to KA (a and b, five animals) or QUIS (d and e, one animal), and to visual responses (c, same five animals as a and b) (ordinates). All are shown as functions of distance anterior to cannula delivering APV (abscissae). c includes 79 sites (69 in APV hemispheres, 10 in control hemispheres) at which only activity was studied, as well as 123 sites (95 in APV hemispheres, 28 in control hemispheres) at which both activity and drug thresholds were studied. In QUIS animal, penetrations 8.3 mm anterior to cannula and in control hemisphere were both controls for normalization of thresholds and statistical tests. Conventions for Figs. 2 and 4: NMDA and KA or QUIS currents for each animal and each electrode have been normalized to the mean threshold current seen in the control hemisphere for that drug, electrode, and animal. For a, b, d, and e, histogram bars show mean, error bars indicate ±SEM, and numbers above error bars indicate number of sites. For c, bars represent percent of sites in each bin with indicated activity: ▨, activity ratings 0–2 (lacking reliable visually driven activity); ■, activity ratings 4–5 (vigorous visual responses). Difference from 100% in each bin is made up by sites with activity rating 3. Numbers above bars indicate total number (100%) of sites. Statistical significance of elevation of thresholds (a, b, d, and e) or depression of activity (c), in comparison to control data, was assessed by Kolmogorov–Smirnov two-sample test or Mann–Whitney U test or, for c only, by χ^2 test. ∗∗∗, $P < 0.001$; ∗∗, $P < 0.01$; ∗, $P < 0.05$.

of the NMDA threshold to ensure a blockade of NMDA receptors, vigorous activity was nearly absent (c). Cells with vigorously driven activity were found in the APV-treated hemisphere at only 3 of 38 sites where thresholds were elevated by more than two standard deviations above the control side mean, and at only 1 of 30 sites where thresholds were elevated by more than 3.2 standard deviations. In contrast, at 29 of 38 control sites, and at 20 of 28 sites in APV-treated cortex with thresholds less than one standard deviation above the control side mean, cells responded vigorously to visual stimulation. We conclude that a sufficiently complete NMDA blockade virtually abolishes normal, vigorously driven neuronal activity.

Identical treatment in three animals with the inactive stereoisomer L-APV did not suppress activity (except in regions within 750 μm of the cannula, where mechanical damage was possible), indicating a stereospecific effect. L-APV treatment did not elevate NMDA or KA thresholds at any distance studied.

DISCUSSION

The preceding demonstrates that infusion of APV at a concentration sufficient to specifically block the NMDA receptors of all cells at a site leads to profound suppression of cortical activity. The measure of NMDA threshold used here is the current at which at least one cell in the local population begins to respond to NMDA application. Similarly, the measure of activity deems sites to have vigorous responses if at

least one cell in the local population responds vigorously to visual stimulation. Thus, at sites where at least one cell responded normally to NMDA, at least one cell generally responded vigorously to visual stimuli; while conversely, at sites where no cell responded normally to NMDA, in general no cell responded vigorously to visual stimuli.

Several observations indicate that the suppression of cortical activity produced by APV infusion was due to a specific blockade of NMDA receptors. The fact that no such suppression was seen with infusion of L-APV demonstrates that the effect is stereospecific. A stereospecific action of D-APV at non-NMDA glutamate receptors does not appear to play a role for two reasons. First, no elevation of either QUIS or KA threshold was seen even at the closest distances to the cannula or at the highest NMDA thresholds. Concentration decreased many times, as judged by decrease of NMDA thresholds, within the regions in which suppression of activity was seen. Therefore even if slight, undetected effects on QUIS or KA receptors occurred at the closest distances, there should have been no such effects at further distances where activity suppression persisted. Second, if the activity blockade were due to a nonspecific effect seen only at high APV concentrations, we would expect to have found a region with markedly elevated NMDA thresholds but normal activity. Instead, activity was very poor wherever NMDA thresholds were elevated (Fig. 4c).

An additional argument reinforces these conclusions. L-APV, which is a weak blocker of NMDA receptors, did not
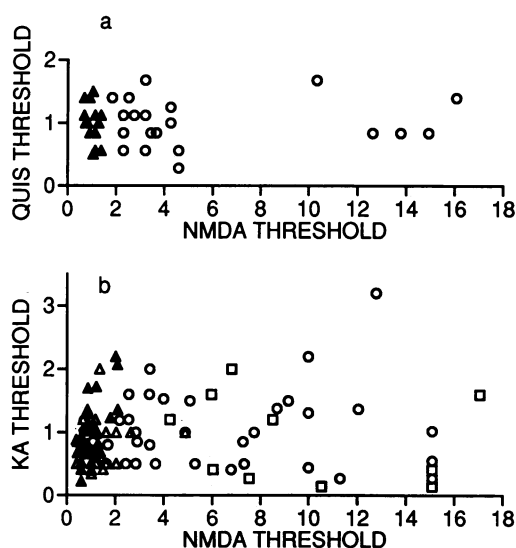
FIG. 3. Comparison of QUIS (*a*) or KA (*b*) thresholds to NMDA thresholds on a site-by-site basis, for the data shown in Figs. 2 and 4. Symbols code distance of a site from the cannula: ▲, control hemisphere or >7 mm anterior to cannula; △, 4–7 mm anterior to the cannula; ○, 1–4 mm anterior; □, 0–1 mm anterior to the cannula. Thresholds normalized as in Fig. 2.

elevate NMDA thresholds even 0.5 mm from the cannula. Based on pharmacology of spinal cord cells, this indicates that the highest concentrations of APV achieved with our protocol, at the closest distances to the cannula studied, were at most ⅛ (with D-APV) or ¹⁄₂₀ (with DL-APV) of that required to block either QUIS or KA receptors (17, 18).¶

We have found a critical role of the NMDA receptor in excitatory transmission in the adult: at sufficiently elevated NMDA thresholds, normal visual responses are nearly abolished. In contrast, Tsumoto and colleagues (12, 13) found that, while local iontophoretic application of APV significantly suppressed visual responses in 71% of cells studied in kitten visual cortex, only 34% of cells in adult cat visual cortex were significantly suppressed. Most or all of these cells did not have visual responses completely suppressed. More recent results suggest that iontophoresis of APV in adult animals suppresses visual responses of many cortical cells in superficial layers but of few cells in granular and deep layers (19), although the previous work found the strongest suppression in layer 5 (13).

We see two probable explanations for the discrepancy between these results and ours. First, our method suppresses both cells that are directly dependent on NMDA receptors for their activation and cells that are indirectly dependent via corticocortical connections, whereas iontophoresis affects only a very local region of cortex. The suppression of deep layer cells we have found cannot be explained simply by the suppression of superficial layer cells (19), since silencing of superficial layers by cortical cooling, or destruction of them by cryogenic lesions, leaves the responses of deep layer cells intact (20). Methods of widespread drug application (21, 22) such as the one we have used are necessary for long-term studies of the role of NMDA receptors in development, plasticity, and overall cortical function.

¶The potency (higher numbers represent weaker effects) of DL-APV as an antagonist of NMDA is 1.9 (17), and that of L-APV is 31 (18), relative to D-APV = 1.0 as an antagonist of NMDA. The potencies of D-APV as an antagonist of KA and QUIS, respectively, are 455 and 236; while those of DL-APV as an antagonist of KA and QUIS, respectively, are 724 and 333 (17). Our statement in the text results from the calculation that 31/236 ≈ ⅛, while (31/1.9)/333 ≈ ¹⁄₂₀.
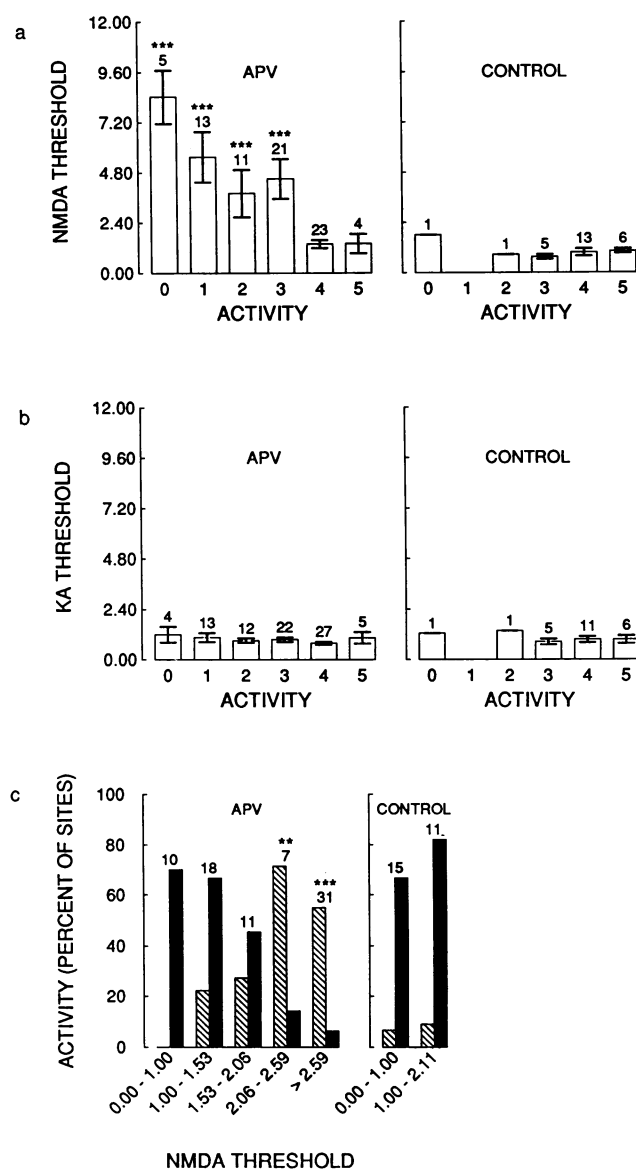

FIG. 4. Site-by-site comparisons of thresholds with activity. Conventions as in Fig. 2. (*a*) NMDA threshold as a function of multiunit activity rating. (*b*) KA threshold as a function of multiunit activity rating. (*c*) Multiunit activity rating as a function of NMDA threshold. Bins on the APV side represent standard deviations (0.53) above the control side mean threshold of 1.0. Points above 1.0 on the control side have been collapsed into a single bin, as only three points had threshold elevated by more than one standard deviation. Because of the possibility of nonspecific damage very close to the cannula, this figure includes only data from sites >1 mm anterior to the cannula. The 12 excluded sites at distances ≤1 mm all had activity ratings ≤3 and NMDA thresholds ≥4.26; their inclusion would only have made the results appear to support our conclusions more strongly.

Second, individual cells may see lower and less uniform concentrations of APV with iontophoretic application. Iontophoresis produces an extreme spatial gradient of concentration, varying strongly over 100 μm (19, 23). In contrast, cortical dendrites may extend over many hundreds of μm from the cell body (24, 25). Thus iontophoresis of APV may fail to block NMDA receptors completely over the entire dendritic tree of the cell being studied. Incomplete blockade may also be produced by iontophoretic application if synaptic concentrations of NMDA are much larger than the concentrations achieved by NMDA iontophoresis, since blockade of the response to NMDA iontophoresis is used to calibrate the

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iontophoretic currents of APV. In some systems, it has been shown that substantially greater APV currents may be needed to block the synaptic responses mediated by NMDA receptors than to block responses to NMDA iontophoresis (26, 27). Incomplete blockade may be indicated by Tsumoto and colleagues' report (12) that, in the same adult cats in which the effects of APV iontophoresis were studied, visual responses were suppressed in only 71% of cells by iontophoretic application of kynurenate [which abolishes synaptic EPSPs and responses to all glutamate agonists in cultured cells (1) and slices (2) of visual cortex].

We studied cells after exposure to APV for 1 day. Iontophoretic methods study acute application. Hence, receptor regulation in response to blockade may play a role in the greater degree of activity suppression that we see.

Our results indicate that NMDA receptors participate in, and are required for, the normal responses of many mature visual cortical cells. The NMDA receptor mediates a slow, long-lasting EPSP (4–11) that rises to peak in 10–75 msec (4–7, 10–11). This slow EPSP is seen under physiological conditions particularly in response to high-frequency stimulation (7–9). Visual cortical cells receive appropriately high-frequency and maintained inputs (28) to evoke such a slow EPSP, and they integrate these inputs over long and varied time periods: latencies between responses in lateral geniculate nucleus and visual cortex are greater than 20 msec (29), compared to conduction times of 2–3 msec. Thus, visual cortical responses may depend upon the buildup of a slow baseline depolarization mediated by NMDA receptors. Such a slow EPSP could provide a base upon which continuing subthreshold input, mediated by non-NMDA receptors, would become suprathreshold. Intracellular recordings of responses of visual cortical cells to stimulation by light show a similar time course: a slow (15- to 60-msec) baseline depolarization must build before individual fast EPSPs become suprathreshold, and this depolarization persists throughout the postsynaptic spike response (28). This depolarization was attributed to summation of fast EPSPs, but results in other systems (5, 7) demonstrate that such apparent summation can represent slow, NMDA-activated EPSPs, abolished by APV.

There is clear precedent for involvement of NMDA receptors in normal, mature sensory activation. In ventrobasal (somatosensory) thalamus, APV antagonizes responses to maintained sensory stimulation, but not to transient sensory stimulation (30, 31). More recently, a preliminary report that sensory activation of visual thalamic cells depends upon NMDA receptors has appeared (32). In hippocampus, it is known that NMDA receptors can carry a significant fraction of the synaptic current (4), and are involved in responses to sustained (7, 8), but not transient (33, 34), electrical stimulation. Little is known of the role of NMDA receptors in hippocampal responses to natural events. In general many factors, including local excitatory and inhibitory circuitry and the strength and temporal pattern of afferent activation, may determine whether excitatory transmission depends upon NMDA receptors in a particular location and situation. In this regard, it may be of interest for cortical transmission that there appears to be a thalamic system capable of modulating NMDA receptor activation in deep layers of cortex in a widespread, diffuse manner (35).

Chronic application of APV has been shown to prevent or reverse activity-dependent developmental plasticity in the visual system (21, 22). It is, however, well known that disruption of the pattern of activity can itself profoundly alter plasticity (discussed in ref. 36). Visual responses in cortex are more strongly suppressed by APV iontophoresis in kittens than in adult cats (12, 19). Thus, chronic APV application in kittens is likely to suppress activity at least to the degree that we have found in adults, wherever concentrations become sufficient to

block NMDA receptors.|| The same may be true in other developmental systems. Hence, the developmental results may reflect the effects of suppressing postsynaptic activity, rather than of specifically blocking a mechanism of plasticity.

In visual and perhaps other regions of cortex, integration over times comparable to that of NMDA-mediated slow EPSPs appears to be the normal mode of response to natural stimuli. Patterns of activation among inputs which are high-frequency and maintained over many tens or hundreds of milliseconds are also the norm. NMDA receptors may thus be used, at various locations and times, for either or both of two distinct tasks: to regulate synaptic plasticity, and to regulate the temporal patterns of input that can activate postsynaptic cells.

||Activity must be studied as a function of the degree of NMDA receptor blockade as well as of time. The spatial gradient of APV varies with different infusion durations and among animals. Also, receptors may regulate in response to extended periods of blockade. Hence, it is impossible to relate neuronal activities in other studies (21) simply to distance from the APV cannula.

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