N-Methyl-D-Aspartate Receptors Contribute to Excitatory Postsynaptic Potentials of Cat Lateral Geniculate Neurons Recorded in Thalamic Slices

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N-Methyl-D-aspartate receptors contribute to excitatory postsynaptic potentials of cat lateral geniculate neurons recorded in thalamic slices

(excitatory amino acid/corticogeniculate/low-threshold calcium spike/optic tract/retinogeniculate)

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ABSTRACT **Neurons of the cat's dorsal lateral geniculate nucleus were recorded intracellularly to study the contribution of *N*-methyl-D-aspartate (NMDA) receptors to excitatory postsynaptic potentials (EPSPs) and low-threshold calcium spikes. EPSPs were evoked by stimulation of retinogeniculate axons in the optic tract and/or corticogeniculate axons in the optic radiations; EPSPs from both sources were similar. These EPSPs had one or two components, and the second component had several characteristics of NMDA receptor-mediated events. For example, EPSP amplitude decreased when neurons were hyperpolarized and increased when stimulus frequency was increased; these EPSPs could also be blocked reversibly by application of the selective NMDA receptor antagonist DL-2-amino-5-phosphonovaleric acid (APV). We also studied the influence of NMDA receptors on low-threshold calcium spikes, which are large, voltage- and calcium-dependent depolarizations that are often accompanied by high-frequency action potential discharge. APV blocked synaptically activated low-threshold calcium spikes, but APV had no effect on low-threshold calcium spikes that were elicited by current injection. Therefore, APV does not appear to have a direct effect on the T-type calcium channel that is involved in generation of low-threshold calcium spikes. The voltage and frequency dependence of the NMDA receptor-mediated component of the EPSPs, as well as its ability to trigger low-threshold calcium spikes, provide for complex signal processing in the lateral geniculate nucleus.**

To examine mechanisms underlying retinogeniculate and corticogeniculate transmission, we used a slice preparation to record from geniculate neurons intracellularly while stimulating the retinal or cortical input. Of specific interest was the possible role of *N*-methyl-D-aspartate (NMDA) receptors in generating excitatory postsynaptic potentials (EPSPs), since activation of this receptor is associated with complex events (5–7). Thus, we compared EPSPs of geniculate neurons with the distinctive characteristics of NMDA-mediated EPSPs that have been described in other preparations. For example, in rat neocortex (8, 9) and hippocampus (10–12), NMDA receptor-mediated EPSPs contribute a component to the EPSP that peaks at a relatively long latency after the stimulus. This late component decreases in amplitude upon membrane hyperpolarization, a phenomenon attributed to the voltage-dependent block by magnesium ions of the ion channel that is coupled to the NMDA receptor (13, 14). It has also been shown that NMDA receptor-mediated EPSPs are enhanced by increasing frequency of stimulation (8, 12). In addition, NMDA receptor-mediated events may be identified by use of the selective NMDA receptor antagonist DL-2-amino-5-phosphonovaleric acid (APV). Our results suggest that NMDA receptors contribute to retinogeniculate and corticogeniculate transmission and may be one of the factors that provides the lateral geniculate nucleus with the capacity for complex information processing in response to both retinal and cortical inputs.

MATERIALS AND METHODS

Brain slices were made from the lateral geniculate of cats that were deeply anesthetized (0.5–1.0% halothane in a 70:30 mixture of N_2O/O_2), systemically paralyzed (5 mg of gallamine triethiodide followed by 3.6 mg of gallamine triethiodide per hr and 0.7 mg of *d*-tubocurarine per hr), artificially respired via a tracheal cannula, and positioned in a stereotaxic apparatus. To ensure that the cat was adequately anesthetized and maintained in stable condition, electrocardiograms, electroencephalograms, end-tidal CO_2, and body temperature were continuously monitored.

A rectangular area of skull overlying the right lateral geniculate nucleus was removed, and a block of tissue containing the lateral geniculate nucleus (≈1.5 cm anteroposteriorly and 3 cm mediolaterally) was excised and immediately placed in ice-cold buffer (124 mM NaCl/5 mM KCl/2 mM $CaCl_2$/1.0 mM $MgSO_4$/1.25 mM NaH_2PO_4/26 mM $NaHCO_3$/10 mM dextrose, pH 7.4). Coronal slices (400 μm thick) were cut from the block of tissue with a vibratome while the entire block was immersed in cold, oxygenated buffer. Slices were immediately placed on a nylon mesh in a recording chamber at an interface of warmed (34°C), oxygenated (95% O_2/5% CO_2) air and buffer.

Neurons in layers A and A_1 of the lateral geniculate nucleus (Fig. 1*A*) were impaled with glass microelectrodes (capillary-filled borosilicate glass, 50–120 MΩ resistance, and filled with 4 M potassium acetate or 1–2% Lucifer yellow CH in 1 M LiCl). We saw no differences in electrophysiological properties or in synaptic potentials when using these different electrolytes. A high-input impedance amplifier with a bridge circuit was used (Axoclamp-2A). Stimulation of afferent pathways consisted of brief current pulses (0.1–0.5 mA; 20–200 μs; typically 0.3 Hz) using a bipolar stimulating electrode (twisted, Teflon-coated, stainless steel wires; each wire diameter, 50 μm). The stimulating electrode was placed on the slice surface, in the area of the optic tract or optic radiations, >100 μm from the lateral geniculate nucleus and >500 μm from the impaled cell (Fig. 1*A*). APV (Sigma) was applied in small droplets (<100 μl of 1 mM APV dissolved in 0.9% NaCl to the slice surface, or added to the perfusate as 25 μM or 50 μM, dissolved in buffer).

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Abbreviations: NMDA, *N*-methyl-D-aspartate; EPSP, excitatory postsynaptic potential; APV, DL-2-amino-5-phosphonovaleric acid; IPSP, inhibitory postsynaptic potential.

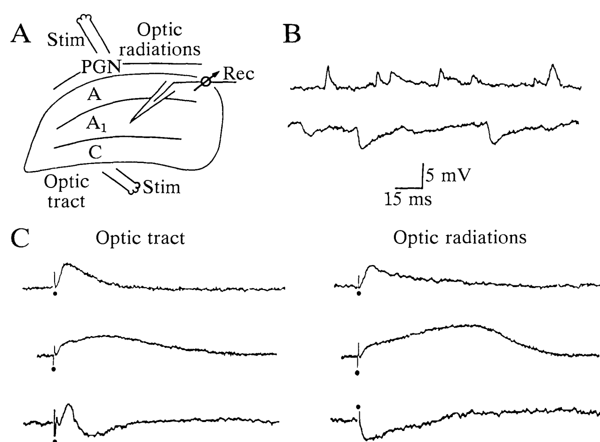

FIG. 1. Schematic diagram of the cat lateral geniculate slice preparation and representative examples of responses to synaptic activation of optic tract and optic radiations. (*A*) Schematic of the slice preparation illustrates typical sites for recording (REC) and stimulating (STIM) electrodes. The borders of the lateral geniculate nucleus and its major subdivisions (A, lamina A; A_1, lamina A_1; C, C laminae) are shown, as well as the location of the perigeniculate nucleus (PGN). (*B*) Examples of spontaneous PSPs (upper trace: membrane potential, −80 mV; lower trace: membrane potential, −48 mV) are shown for two different geniculate neurons. (*C*) (*Left*) Representative examples of synaptic potentials elicited by stimulating the optic tract are illustrated. Each response was elicited from a different cell. Membrane potentials were as follows: top trace, −60 mV; middle trace, −58 mV; bottom trace, −56 mV. Synaptic stimulus artifacts are clipped and are indicated by dots. (*Right*) Examples of responses to stimulation of the optic radiations recorded from three different cells. Membrane potentials were as follows: top trace, −59 mV; middle trace, −58 mV; bottom trace, −55 mV. Calibration is the same as in *B*.

To determine input resistance, the voltage response at steady state (measured at the end of 150-ms duration current steps injected through the recording electrode) was plotted as a function of current amplitude. Input resistance was calculated from the slope of the linear portion of the current–voltage relation. Unless otherwise indicated, the Mann–Whitney *U* test was used for all statistical comparisons. Values are presented (see below) as the mean ± SEM.

RESULTS

All 55 cells included in this study had resting potentials >55 mV (−61 ± 1 mV), overshooting action potentials (81 ± 1 mV), and input resistances >30 MΩ (49.6 ± 3.6 MΩ). Most cells showed spontaneous PSPs (Fig. 1*B*). The voltage dependence of these PSPs suggested that they were inhibitory PSPs (IPSPs) (Fig. 1*B*).

Subthreshold responses to stimulation of either optic tract or optic radiations produced EPSPs, IPSPs, or a mixed response consisting of an EPSP followed by an IPSP (Fig. 1*C*). For the 41 cells in which responses to stimulation of optic tract were tested, EPSPs were recorded in 18 cells, IPSPs were elicited in 5 cells, EPSPs followed by IPSPs occurred in 6 cells, and in the other 12 cells no response could be elicited. Of the 23 cells that were tested for responses to stimulation of the optic radiations, EPSPs were evoked from 15 cells, EPSPs followed by IPSPs occurred in 2 cells, 1 cell produced only an IPSP, and in the remaining 5 cells no response could be evoked. A total of 64 responses to stimulation were recorded from 55 cells (9 of the 55 cells were stimulated at two different sites; the others were stimulated at only one site). The lack of responses in some cells, and the paucity of IPSPs relative to studies of geniculate neurons *in vivo* (15–18), probably reflects that many axons that terminate on geniculate neurons *in vivo*, especially those that are inhibitory, were severed during slice preparation.

Unimodal vs. Bimodal EPSPs. Depolarizations that were graded in amplitude and could trigger action potentials are referred to as EPSPs. These EPSPs differ from another type of depolarization known as the "low-threshold calcium spike" (described more fully below), chiefly on the basis of the narrow membrane voltage range within which low-threshold spikes can be elicited. Measurements of EPSPs refer to EPSPs elicited with stimulus intensities that were just below threshold for action potential generation and were elicited between membrane potentials −50 and −60 mV.

Of the 34 EPSPs that had no IPSP component, 12 EPSPs had one peak ("unimodal") and 22 EPSPs had two peaks ("bimodal"). In most cells, the number of peaks of EPSPs did not change if stimulus frequency was increased. But in 5 of the 34 cells, EPSPs were unimodal at low stimulus frequencies (0.3–0.5 Hz) and bimodal (a second, later peak was evident) at higher stimulus frequencies (1–10 Hz). In terms of waveform and voltage sensitivity (see below), the first component of the bimodal EPSPs closely resembled unimodal EPSPs, but we have not yet categorized unimodal EPSPs in detail and therefore consider only bimodal EPSPs in the analysis below. All synaptic responses were tested at depolarized membrane potentials (−50 to −60 mV) to identify whether an IPSP component was present; if an IPSP was present, the response was not included because of the complication of the IPSP component in interpreting EPSPs.

Bimodal EPSPs. The first (or "early") peak of bimodal EPSPs occurred within 10 ms of the stimulus (times to peak: optic tract, 5.8 ± 0.9 ms; optic radiations, 6.2 ± 0.7 ms; Fig. 2*A*). The second (or "late") peak occurred at least 10 ms after the stimulus, and the late peak was prolonged—i.e., the peak had a slow rising phase and the peak amplitude was maintained for 10–50 ms before beginning to decay (Fig. 2*A*). The midpoint of the late peak was 19.1 ± 2.4 ms for stimulation

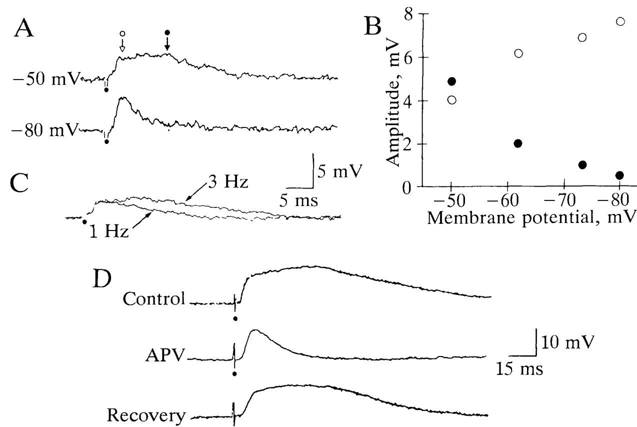

FIG. 2. Voltage dependence, effects of stimulus frequency, and sensitivity to the NMDA receptor antagonist APV of bimodal EPSPs. (*A*) Responses to stimulation of optic radiations are shown at two different membrane potentials. Open arrow indicates the point where the amplitude of the early peak of the EPSP was measured; solid arrow indicates the point where the late phase was measured. Dots below the traces mark stimulus artifacts, which are clipped. (*B*) The amplitude of the EPSPs shown in *A*, measured 5 ms (○) and 20 ms (●) after the stimulus artifact, are plotted as a function of membrane potential. (*C*) Two responses to optic tract stimulation are shown, evoked during stimulation at 1 Hz, and 30 ms after a train of five stimuli at 3 Hz. This was a different cell from the one in *A*, but the calibration is the same as in *A*. Membrane potential, −57 mV. (*D*) Synaptic response to stimulation of optic radiations is shown immediately prior to application of APV (control, top trace), 5 min after perfusion in 50 μM APV (APV, middle trace), and 45 min after application of APV (Recovery, bottom trace). This was a different cell from the ones in *A* and *B*. Membrane potential, −60 mV.

of optic tract and 27.2 ± 4.6 ms for stimulation of optic radiations. The mean amplitude of the early peak was 7.5 ± 1.3 mV for optic tract stimulation and 5.4 ± 0.7 mV for stimulation of optic radiations. The amplitude of the late component was variable (see below), so the maximum amplitude seen was used for all measurements. The mean of these maximum amplitudes for the late peak was 8.4 ± 0.7 mV for optic tract stimulation and 6.8 ± 1.5 mV for stimulation of optic radiations. The latencies and amplitudes of the early and late components of bimodal EPSPs were not correlated ($r < 0.1$; $P > 0.1$ for all correlations), which suggests that these components represent independent events. There were no significant differences ($P > 0.1$) between EPSPs evoked by optic tract vs. optic radiation stimulation in the latencies to peak and the peak amplitude. Therefore, bimodal EPSPs elicited by optic tract and optic radiation stimulation were grouped together for the description below.

Voltage dependence of EPSPs. Of the 22 cells in which bimodal EPSPs were elicited, membrane potential was systematically varied between −50 and −85 mV in 14 cells. The early peak of bimodal EPSPs increased in amplitude upon hyperpolarization in 9 cells and did not change appreciably in amplitude in the other 5 cells. The late peak decreased in amplitude with hyperpolarization in all 14 cells (Fig. 2 *A* and *B*). There are several possible explanations for the fact that the early peak of the EPSP was unaffected by membrane potential in 5 cells. First, the site of synaptic input that underlies the early peak might be too distant electrotonically from the soma, and thus injected current in those cells may not have been effective in changing the membrane potential at the site of synaptic input. Another explanation is that there was sufficient overlap of the two phases of the EPSPs so that the opposite voltage dependence of the late phase masked the voltage dependence of the first phase.

Effect of stimulus frequency. At low stimulus frequencies (0.3–0.5 Hz), the amplitude and latency of the early peak of the bimodal EPSP was quite stable in its amplitude and time to peak from stimulus to stimulus. However, the late peak varied in amplitude and latency.

At higher stimulus frequencies (1–10 Hz for 1–15 s), the early peak did not change or increased slightly in amplitude (Fig. 2*C*). The late peak increased in amplitude and/or duration but was still variable (Fig. 2*C*). The increase in the late peak lasted for several seconds after returning to low stimulus frequency. As mentioned above, in 5 of the 22 cells in which bimodal EPSPs were observed, the late peak was not clearly evoked unless stimulus frequency was >1 Hz.

Sensitivity of the late peak of the bimodal EPSP to APV. Application of one drop of 1 mM APV (three cells) or perfusion of 25 or 50 μM APV (one cell tested at each concentration) blocked the late peak and decreased the duration of the bimodal EPSP without affecting the amplitude, time to peak, or waveform of the early peak of the EPSP (Fig. 2*D*; see also Fig. 4*A*). These effects were reversible within 5–50 min of APV application, and in two of the five cells in which it was attempted, the effect was reproduced after a second application of APV. APV had no effect on input resistance in any of the five cells and no effect on resting membrane potential in four of the five cells; the fifth cell depolarized 4 mV as a drop of APV was applied to the slice surface and after 1 s, the resting potential returned to the pre-APV resting potential. In two cells where synaptic potentials that were not bimodal EPSPs were elicited (a short latency, unimodal EPSP was elicited in one cell and an IPSP in a second cell), APV had no effect on the synaptic response, even when >5 drops of APV was applied.

Low-Threshold Calcium Spikes. It has been shown that small injections of depolarizing current to thalamic neurons at hyperpolarized potentials can trigger a large depolarization that is triangular in shape and calcium dependent, called a low-threshold calcium spike (20, 21). At membrane potentials more depolarized than about −60 mV, the T-type calcium conductance underlying the low-threshold spike (22, 23) is inactivated, but if the membrane potential is hyperpolarized briefly (so that the membrane potential is approximately −60 to −85 mV for several milliseconds), the calcium conductance becomes deinactivated, and a small depolarization, due to direct current injection or synaptic input, can elicit a low-threshold spike.

Activation of low-threshold spikes by intracellular current injection. In our experiments, low-threshold spikes were elicited directly in all cells by 0.1–0.3 nA, 100-ms depolarizing current pulses at membrane potentials between approximately −60 and −85 mV (Fig. 3*A*). Low-threshold spikes were also evoked upon repolarization following a hyperpolarizing current pulse (Fig. 3*B*).

Synaptic activation of low-threshold spikes. At hyperpolarized membrane potentials (between approximately −60 and −85 mV), stimulation of either optic tract or optic radiations could also elicit low-threshold spikes (Fig. 3*C*). These synaptically activated low-threshold spikes could occur immediately after the early peak of the EPSP (Fig. 3*C*) or >10 ms after the peak of the early EPSP (Fig. 3*C*). Synap-

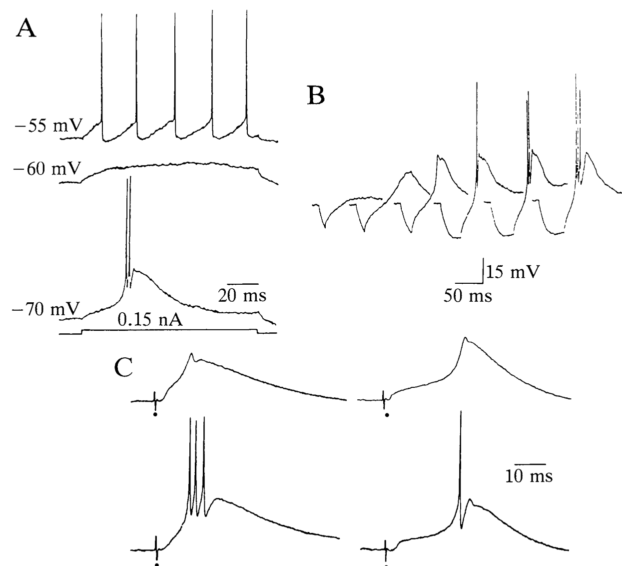

FIG. 3. Low-threshold spikes can be evoked by intracellular current injection or synaptic activation. (*A*) Lateral geniculate neurons possess different firing patterns that depend on membrane potential (20, 21). An intracellular depolarizing current pulse (0.15 nA; 150 ms) was triggered at three different membrane potentials. At the depolarized membrane potential (−55 mV, top trace) a train of action potentials was produced. At the intermediate membrane potential (−60 mV, middle trace) an ohmic response was recorded, subthreshold for action potential generation. At the hyperpolarized potential (−70 mV, bottom trace) a large depolarization was elicited (the low-threshold spike), accompanied by a burst of action potentials. (*B*) Low-threshold spikes followed brief hyperpolarizations. Hyperpolarizing current pulses (0.2 nA; 5–50 ms) were delivered at the resting potential (−63 mV). Note that the amplitude of the low-threshold spike and the number of action potentials that occur on its peak increases as the amplitude and duration of membrane hyperpolarization increases. Action potentials were truncated by digitization of taped data. (*C*) Sample responses are shown to optic tract stimulation (upper trace) and stimulation of optic radiations (lower trace). Note that low-threshold spikes, with (lower trace) or without (upper trace) action potentials riding their crests, occurred at short latencies after the stimulus (*Left*) or at longer latencies (*Right*). The membrane potentials are −63 mV for the upper left trace, −67 mV for the upper right trace, −65 mV for the lower left trace, and −70 mV for the lower right trace.

tically activated low-threshold spikes did not trigger action potentials at low stimulus intensities, but at higher stimulus intensities one to seven action potentials arose on the peak of the low-threshold spike (Fig. 3*C*). Low-threshold spikes were easily differentiated from EPSPs because synaptically activated low-threshold spikes could only be elicited between membrane potentials of approximately −60 to −85 mV. In addition, synaptically activated low-threshold spikes had a completely different waveform than EPSPs (compare Fig. 1*C* with Fig. 3*C*).

Effects of APV on synaptically evoked low-threshold spikes. There were several characteristics that were common to both the late peak of the bimodal EPSP and synaptically evoked low-threshold spikes. For example, their latencies were often similar. In all cases in which a late peak of a bimodal EPSP was elicited at depolarized membrane potentials, stimulation at hyperpolarized potentials evoked a synaptically activated low-threshold spike that occurred at a latency similar to the late peak of the bimodal EPSP (Fig. 4 *A* and *B*). The late peak of the bimodal EPSP and the synaptically evoked low-threshold spike shared a sensitivity to stimulus frequency. In the 5 cells in which late peaks of bimodal EPSPs were only elicited after high-frequency stimulation, low-threshold spikes were only evoked after increasing stimulus frequency also. In the other 17 cells, in which both the late peak of the bimodal EPSP and synaptically activated low-threshold spikes could be evoked by low-frequency stimuli, increasing stimulus frequency increased the amplitude of the late peak of the bimodal EPSP as well as low-threshold spikes. In addition, increasing stimulus frequency often increased the number of action potentials that were triggered at the peak of the synaptically activated low-threshold spike. Interestingly, the effect of stimulus frequency often outlasted the period of high-frequency stimulation (by several seconds) for both the late peak of the bimodal EPSP and the synaptically activated low-threshold spikes.

NMDA receptors may cause a sufficiently large and long-lasting depolarization to trigger synaptically activated low-threshold spikes. In support of this hypothesis, APV application blocked synaptically evoked low-threshold spikes, or increased the stimulus intensity needed to elicit synaptically activated low-threshold spikes, in all four cells tested (Fig. 4*B*). The amplitude and time to peak of the early phase of the synaptic response were unaffected by APV in these four cells (Fig. 4 *A* and *B*). When APV had blocked the synaptically activated low-threshold spike, the waveform and threshold for the nonsynaptic low-threshold spike following hyperpolarizing current injection were unchanged (Fig. 4*C*), arguing against an effect of APV on the T-type calcium channel that is thought to underlie nonsynaptic low-threshold spikes (22, 23). In these four experiments, the waveform of low-threshold spikes evoked by intracellular current injection, the amount of depolarizing current necessary for activation of the low-threshold spike, and the degree of hyperpolarization necessary for deinactivation (Fig. 4*C*) were all monitored throughout the course of the experiment, and no changes were found in any of these parameters. We tested this with a range of current pulse amplitudes (±0.05 to ±0.5 nA; 50- to 150-ms duration) before and after APV application and never detected any effects of APV on the low-threshold spikes so activated.

DISCUSSION

We have shown that stimulation of the optic tract and/or optic radiations evokes several types of synaptic potentials in neurons of the lateral geniculate nucleus. Stimulation of both regions could evoke an EPSP with two distinct components; NMDA receptors contributed to the late component. Both

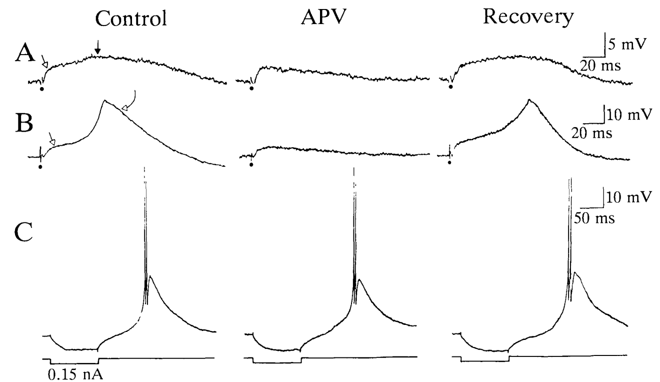

FIG. 4. EPSPs and low-threshold spikes are sensitive to APV. (*A*) Responses to optic tract stimulation of a geniculate neuron are shown. The cell was depolarized to −49 mV. Left trace (Control): a control response was elicited prior to application of APV. The peak of the early phase is indicated by the open arrow and the peak of the late phase is indicated by the solid arrow. Stimulus artifacts are indicated by dots. Center trace (APV): the response to the same stimulus as used in control is shown, elicited 15 s after 1 drop of APV was applied to the slice surface. Note the decrease in the amplitude of the late phase of the EPSP. Right trace (Recovery): a response similar to the control response was elicited 5 min after APV application. (*B*) Responses to the same stimulus as in *A* are shown, when the membrane potential of the cell was −67 mV. Left trace (Control): stimulation prior to APV application evoked a short-latency EPSP (straight arrow) followed by a low-threshold spike (curved arrow). The low-threshold spike did not trigger action potentials. Center trace (APV): the response evoked 10 s after APV application is shown. Note that the low-threshold spike was absent. Right trace (Recovery): 5 min after the application of APV, stimulation evoked a response similar to the control response. (*C*) Responses to intracellular current injection (−0.15 nA; 100-ms pulses) are shown during Control (left trace), just after APV application (center trace), and after Recovery (right trace). Note that APV had no effect on the low-threshold spike activated by current injection.

components can trigger low-threshold spikes, although in our experiments such spikes were more commonly activated by the late component.

Nature of Afferent Axons Activated. We interpret that the EPSPs evoked from optic tract stimulation reflect activity of retinal axons, since there is no known significant axon population in the optic tract other than retinal axons that innervate geniculate neurons. Most EPSPs evoked by stimulation of optic radiations represented activation of corticogeniculate inputs, because the majority of fibers in the optic radiations are corticogeniculate. Corticogeniculate axons outnumber geniculocortical axons by >10:1 (3), and very few axons that exist in the optic radiations arise from brainstem (24). Axons from the perigeniculate and/or thalamic reticular nucleus also exist in the optic radiations, but these are thought to be inhibitory (17, 25, 26) and thus an implausible source of EPSPs. Finally, antidromic responses were rarely elicited after stimulation of optic radiations. The lack of antidromic responses may be due to the slicing of geniculocortical axons, since the axons of all 15 geniculate cells that were filled with Lucifer yellow in slices were directed toward the optic radiations but were cut before they entered the optic radiations (unpublished data).

It is likely that EPSPs evoked by stimulation of optic tract or optic radiations were a product of activation of monosynaptic pathways. This assumption is reasonable because there are no known substantial multisynaptic excitatory pathways that could be triggered by stimulation of the optic tract or optic radiations in the slice preparation. This is an important point in light of the variability often observed in the late peak of bimodal EPSPs, which could be an indication of a polysyn-

aptic mechanism, as opposed to an EPSP produced by monosynaptic activation.

NMDA Receptors and EPSPs. We have not addressed the basis of the early component of the bimodal EPSP but have instead concentrated on the late component. We found that several characteristics of the late component are similar to NMDA receptor-mediated events described in other systems. Specifically, the late peak has a striking voltage dependence in that its amplitude decreases upon membrane hyperpolarization, it is very sensitive to stimulus frequency, and it is blocked by APV. Our results suggest that NMDA receptor activation contributes to the late component of the bimodal EPSP that can be evoked by retinogeniculate or corticogeniculate stimulation.

These results are consistent with extracellular *in vivo* studies in the lateral geniculate showing that cells are sensitive to HA-966 (27), which is an antagonist of the strychnine-insensitive site where glycine binds to the NMDA receptor. Glycine greatly enhances the activity of NMDA receptors (28, 29). These results are also consistent with the finding of a voltage-dependent EPSP in cat geniculate neurons recorded intracellularly *in vivo* (30). Although EPSPs of the rat lateral geniculate were not sensitive to APV, rat geniculate neurons were excited by NMDA application (31). It is possible that species differences could explain why APV-sensitive EPSPs were found in cat but not rat. It should also be pointed out that there are many conditions that must be met in order to activate NMDA receptors synaptically (i.e., membrane potential should be depolarized, extracellular levels of magnesium, glycine, and zinc must be appropriate), so lack of evidence for an NMDA receptor-mediated event must be treated with caution.

Relationship of NMDA Receptors to Low-Threshold Spikes. Our results support that NMDA receptors can trigger synaptically activated low-threshold spikes. Synaptically evoked low-threshold spikes typically occurred at the same latency as the late peak of the bimodal EPSP, were enabled by increasing stimulus frequency, and were sensitive to APV. Although NMDA receptors become blocked at hyperpolarized membrane potentials where low-threshold spikes were deinactivated, it is possible that NMDA receptors are incompletely blocked. Another factor may be the frequency of stimulation, since synaptically activated low-threshold spikes were often elicited only after high-frequency stimulation, which would be expected to potentiate the late phase of the EPSP. After potentiation, the depolarization due to the late peak of the EPSP may have been large enough to trigger a synaptically activated low-threshold spike.

Significance of NMDA Receptors to Retinogeniculate and Corticogeniculate Transmission. If retinal and cortical inputs to the lateral geniculate nucleus activate NMDA receptors, these inputs may have far more complicated effects on geniculate neurons, and thus transmission through the thalamus, than previously thought. First, changes in membrane potential of the geniculate cell will greatly affect the size and duration of the EPSP. This is important because several other nonretinal inputs and neurotransmitters are able to hyperpolarize or depolarize geniculate neurons (1–4, 32). Thus, EPSPs driven by retinal and cortical axons will vary greatly depending on concomitant activity among the other afferents. Second, frequency of excitatory impulses to relay cells will also play a role in the amplitude and duration of EPSPs, since increases in stimulus frequency may selectively enhance the NMDA receptor-mediated component of the EPSP without substantial effects on other components of the EPSP. Third, by triggering low-threshold spikes following synaptic stimulation, NMDA receptors may change the firing pattern of geniculate neurons from tonic firing to burst generation and oscillation. In this role, NMDA receptors not only change the mode of geniculate firing, but also serve as an amplifier of subthreshold EPSPs. Finally, since calcium ions enter the ion channel linked to the NMDA receptor (19), a possible consequence of retinal or cortical excitation of geniculate neurons may be the activation of second messenger systems via increases in intracellular calcium.

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