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Two Distinct Types of Corticothalamic EPSPs and Their Contribution to Short-Term Synaptic Plasticity

Jianli Li, William Guido, and Martha E. Bickford

INTRODUCTION

Corticofugal projections arise from at least two types of cells that differ in their location, morphology, biophysical properties, and axonal projections. Layer V corticofugal cells are large pyramidal neurons that display an intrinsically bursting firing pattern. These cells have long apical dendrites that arborize extensively within layer I and axon projections that innervate a wide array of subcortical areas including the thalamus, pretectum, and superior colliculus. Layer VI corticofugal cells are smaller pyramidal neurons characterized as regular spiking cells (Castro-Alamancos and Connors 1996; Connors et al. 1982; McCormick et al. 1985; Rumberger et al. 1998; Wang and McCormick 1993). These cells have apical dendrites that generally arborize within layer IV and have axonal projections limited largely to the thalamus. In addition, due to diameter differences, the conduction velocity of layer VI axons is much slower than those of layer V axons (Ferster and Lindström 1983; Harvey 1980; Miller 1975; Swadlow et al. 1980; Swadlow and Weyand 1987). The morphology of synaptic terminals originating from these two cells types is also distinct. Layer VI projections, which provide the majority of input to all dorsal thalamic nuclei, are small terminals that innervate the distal dendrites of thalamic neurons (Erisir et al. 1997; Jones and Powell 1969; Li et al. 2003b; Vidnyánszky and Hámori 1994). In contrast, layer V projections, which provide input to a subset of thalamic nuclei, are large terminals that innervate the proximal dendrites of thalamic neurons in complex synaptic arrangements known as glomeruli (Feig and Harting 1998; Li et al. 2003b; Vidnyánszky et al. 1996). The synaptic arrangements of layer V corticothalamic terminals are similar to those of primary sensory afferents, such as retinal terminals in the dorsal lateral geniculate nucleus (dLGN) (Li et al. 2003b; Rapisardi and Miles 1984; Robson and Mason 1979). Thus it has been proposed that layer V corticothalamic terminals may provide the primary or driving input to some thalamic nuclei (Crick and Koch 1998; Sherman and Guillery 1998). One example is the lateral posterior nucleus (LPN), which receives input from both layers V and VI of the visual cortex (Bourassa and Deschenes 1995; Ojima et al. 1996). Nuclei such as the LPN have been termed “higher order” to reflect their close association with cortical circuitry and their possible role in regulating the transfer of signals between cortical areas (Guillery 1995).

However, elaboration of this theory depends on an understanding of the responses of higher-order neurons to stimulation of their cortical inputs. To address this, we studied responses of LPN neurons to stimulation of their corticothalamic afferents. We used repetitive stimulation paradigms as a means to compare properties of LPN corticothalamic EPSPs to those previously reported for retinogeniculate and corticogeniculate (layer VI) EPSPs (Chen et al. 2002; Granseeth and Lindström 2003; Granseeth et al. 2002; Lindström and Wrobel 1990; Turner and Salt 1998; von Krosigk et al. 1999). The current study helps to establish a strong link between thalamic terminal morphology and postsynaptic activity and provides insight into the function of higher order thalamic nuclei.
METHODS

All procedures conformed to National Institutes of Health guidelines for the care and use of laboratory animals and were approved by the University of Louisville Animal Care and Use Committee. For physiology experiments, Wistar rats (Harlan, Indianapolis, IN) ranging from postnatal day 21 to 40 were anesthetized with carbon dioxide and decapitated. The brain was removed and placed in a cold (1–4°C) oxygenated (95%O₂-5%CO₂) solution containing (in mM) 206 sucrose, 2.5 KCl, 1 CaCl₂, 1 MgSO₄, 1 MgCl₂, 1.25 NaH₂PO₄, 26 NaHCO₃, and 10 dextrose, pH 7.4. The brain was cut into two hemispheres at midline, and tissue blocks containing the superior colliculus, thalamus and striatum were further trimmed with a razor blade. Thalamic slices were prepared using a vibratome (Leica, VT1000E, Deerfield, IL) as 400-μm-thick parasagittal sections. Slices were transferred to a temperature-controlled recording chamber (Fine Science Tools, Foster City, CA) and kept perfused with oxygenated artificial cerebrospinal fluid [ACSF, which contained (in mM) 124 NaCl, 2.5 KCl, 1 CaCl₂, 1 MgSO₄, 26 NaH₂PO₄, and 10 dextrose at a pH of 7.4]. Tissue was maintained on a plastic mesh (250 × 250 μm grids) in an interface of warmed (33°C) humidified air (95%O₂-5%CO₂) and oxygenated ACSF. Recordings began 2 h after slices were placed in the recording chamber.

Sharp-tipped electrodes made of borosilicate glass (Sutter Instruments, Novato, CA) and filled with 4M potassium acetate were used to record intracellular voltage responses. Electrodes were pulled horizontally (P97, Sutter Instruments) to a tip-to-tip distance of 250 μm. Intracellular responses were collected in current-clamp mode with a high-impedance amplifier (Axoclamp 2B, Axon Instruments, Union City, CA). Neuronal activity was digitized at 10 kHz (pClamp 8, Axon Instruments) and stored directly on computer.

For each rat, two slices were obtained that included the LPN, and we used size of the adjacent superior colliculus to distinguish the lateral and medial slices. We roughly sketched each slice and documented the recording site locations by using the underlying mesh as a reference. Some LPN cells were also labeled by biocytin injection (Li et al. 2003a) to confirm our recording sites.

To evoke synaptic activity, four micro-concentric tungsten stimulation electrodes (tip diameter: 100 μm, exposed length: 250 μm, tip-to-tip distance: 250 μm, Rhodes Medical Instruments, Tujunga, CA) were placed close to the thalamic reticular nucleus (TRN) as shown in Fig. 1B. A brief constant current pulse (50-μs duration) was produced by a stimulator (Grass S88, Grass Instrument, W. Warwick, RI) that was connected to a stimulus isolation unit (World Precision Instruments A365, Sarasota, FL) which controlled current intensity produced by a stimulator (Grass S88, Grass Instrument, W. Warwick, RI). Neuronal activity was digitized at 10 kHz (pClamp 8, Axon Instruments) and stored directly on computer.

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We assume that our recordings were from relay cells because they exhibited a robust low-threshold calcium conductance and hyperpolarization-activated mixed cation conductance (Li et al. 2003a). When the resting membrane potential (RMP) of each LPN cell was more negative than Δ-68 mV, corticothalamic EPSPs could evoke low-threshold calcium spikes (LTSs). An example of this is shown in Fig. 1D. To observe EPSPs in the absence of LTS or action potentials, the RMP of each recorded cell was maintained at a level between their two thresholds of activation simply by injecting DC current through the recording electrode. In addition, if one stimulating electrode evoked an antidromic response, we switched to another stimulating electrode to evoke orthodromic responses or abandoned the recording.

The GABAₐ antagonist bicuculline (20 μM, Sigma, St. Louis, MO), and the GABAₐ antagonist CGP55845 (5 μM, Tocris, Ellisville, MO) were routinely added to the perfusing buffer to block all inhibitory synaptic activity in the LPN. To study the pharmacology of the corticothalamic projection, the N-methyl-D-aspartate (NMDA) glutamate receptor antagonist 2-amino-5-phosphonovalerate (APV, 25 μM, Sigma) and non-NMDA glutamate receptor antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX, 20 μM, Sigma) were added to the bath.

Quantitative results are expressed as means ± SD. Paired or unpaired Student’s t-test were used to test for statistical significance between data sets.

To study the distribution and morphology of corticothalamic terminals in the LPN, two rats were anesthetized with intraperitoneal injections of pentobarbital sodium (initially 50 mg/kg, with supplements injected as needed to maintain anesthesia) before they were placed in a stereotaxic apparatus and prepared for surgery. Biotinylated dextran amine (BDA; 5% in deionized water) was injected into cortical area 17 with a Hamilton syringe. Two injections (0.1 μl each) were placed at depths of 1.0 and 1.5 mm ventral to the cortical surface. After a survival time of 1 wk, the rats were perfused transcardially with ACSF followed by a fixative solution of 4% paraformaldehyde in 0.1 M phosphate buffer (PB).

The fixed brains were cut into 400- or 100-μm-thick parasagittal sections using a vibratome and collected in PB. After preincubation in 10% normal goat serum (NGS) in phosphate-buffered saline (PBS; 0.01 M PB with 0.9% NaCl, pH 7.4) for 30 min, sections that contained BDA were incubated overnight at room temperature in a 1:50 dilution of avidin and biotinylated horseradish peroxidase (ABC; Vector, Burlingame, CA) in PBS, with 1% NGS and 0.5% Triton X-100. After buffer washes, sections were reacted with nickel-intensified diaminobenzidine (DAB) for 10–30 min. After PB washes, sections were mounted on slides, dehydrated, and coverslipped for light level examination.

RESULTS

Two types of corticothalamic terminals in LPN slices

We injected BDA into cortical area 17 and then cut the fixed thalami into 400-μm-thick slices, similar to those used for in vitro experiments. We found that from the caudal/medial visual cortex, corticothalamic fibers travel rostrally and laterally to gain access to the thalamus through the internal capsule. As shown in Fig. 1A, two different types of cortical terminals were labeled in the LPN (see also Li et al. 2003b). Small type I terminals were observed throughout the LPN and LGN (data not shown). Type I terminals are small boutons on short stalks that emanate from long lengths of fine caliber axons. Type II terminals, present only in the LPN, are large boutons that form discrete clusters. Type II terminals arise from axons of much larger caliber than those that give rise to type I terminals. In the rostral LPN, most type II terminals were distributed in regions that also contained type I terminals (Fig. 1A, I+II). However, isolated clusters of type II terminals were observed within the rostromedial regions of the LPN (Fig. 1A, II, inset). Figure 1A also illustrates that type I terminals far outnumber the type II terminals.

Two distinct types of EPSPs are elicited by stimulation of corticothalamic fibers

Stimulation of corticothalamic fibers evoked two distinct types of EPSP in LPN neurons. The first (type I) EPSP showed a facilitation in response to repetitive stimulation for frequencies >0.5 Hz (Fig. 2, A and B, n = 46). Type I EPSPs were the
most commonly encountered responses. In some cases, more than one of the four stimulating electrodes could evoke type I responses (of different amplitude) in single LPN neurons. The second (type II) EPSP showed a frequency-dependent depression after stimulation of corticothalamic fibers at frequencies >0.5 Hz (Fig. 3, A and B, n = 9). Type II EPSPs were more rarely encountered, and for any given LP neuron, only one of the four stimulating electrodes could elicit a type II response.

Several other parameters of the type I and II EPSPs differed. First, as the stimulation intensity was increased, the amplitude of type I EPSPs increased in a graded fashion, and a decrease in latency was detected at the highest stimulus intensities (Fig. 2C). In contrast, the amplitude of type II EPSPs remained constant once the threshold for initiation had been reached, and the latency remained relatively constant (Fig. 3C). In addition, the latencies of type I EPSPs (4.3 ± 0.8 ms, n = 46) were significantly slower than those of type II EPSPs (1.6 ± 0.5 ms, n = 9, P < 0.001) and the rise time (10–90% of maximum amplitude) of type I EPSPs (4.1 ± 1.6 ms, n = 20) was significantly slower than that of type II EPSPs (1.1 ± 0.5 ms, n = 9, P < 0.001). Finally, the average type I EPSP amplitude (at threshold) was much smaller than that of the average type II EPSP amplitude (type I: 0.8 ± 0.2 mV, n = 11; type II: 8.2 ± 3.7 mV, n = 9). As illustrated in Fig. 4, EPSP threshold amplitudes were correlated with EPSP latency.

Paired-pulse stimulation

Further features of the type I and II EPSPs were explored using a paired-pulse stimulation protocol. After determining

FIG. 1. The distribution and morphology of corticothalamic fibers and corticothalamic excitatory postsynaptic potentials (EPSPs). A: the lateral posterior nucleus (LPN) contains 2 distinct morphological types of corticothalamic terminals. Shown is a 400-μm-thick parasagittal section that contains corticothalamic axons and terminals labeled by an injection of biotinylated dextran amine into area 17. Scale bar = 50 μm. Most corticothalamic axons (type I) are very fine axons that give rise to small boutons that are distributed along long lengths of axon. Shown is a camera lucida drawing of type I terminals contained within a 50-μm-thick section. Scale bar = 10 μm. A small subset of corticothalamic axons (type II) are much thicker and give rise to clusters of large boutons. Shown is a camera lucida drawing of type II terminals contained within a 400-μm-thick section. Regions within the slice that contain predominately type I terminals, type II, or both (I+II) are indicated. Inset: type II axons within the section photographed using higher magnification. B and C: 2 400-μm-thick sections from each hemisphere were used for recordings. Scale bar = 1 mm. The distribution of recorded LPN neurons is shown for lateral (B) and medial (C) sections. The locations of the stimulating electrodes, near the thalamic reticular nucleus (TRN), are represented by dark blue circles. The location of cells that responded to the stimulation of corticothalamic fibers with type I EPSPs are represented with white dots, those that responded with type II EPSPs with red dots, and those that had mixed responses with yellow dots. D: a corticothalamic EPSP is evoked during stepwise current injection. When the membrane potential is depolarized, the EPSP elicits an action potential (peak trimmed). When the membrane potential is hyperpolarized, the EPSP elicits a low-threshold calcium spike (LTS), which triggers action potentials. SC, superior colliculus; LTN, lateral thalamic nucleus.
the EPSP threshold, pairs of stimuli were separated by 100–4,000 ms. As illustrated in Fig. 5A, for type I EPSPs, the second response of each pair was enhanced after interstimulus intervals ≤2,000 ms (0.5 Hz). The peak increase in EPSP amplitude could be fitted to an exponential curve (Fig. 5B). Interestingly, we also observed that the latency of the second EPSP decreased significantly at the shortest interstimulus intervals (from 4.2 ± 0.9 to 3.6 ± 0.8 ms at interstimulus intervals of 100 ms, \( P < 0.001 \), \( n = 26 \); Fig. 5, C and D).

In contrast, for type II EPSPs, the second response of each pair was decreased after interstimulus intervals ≥2,000 ms (Fig. 6A). No decrease was observed when the pairs were separated by ≥4,000 ms. As illustrated in Fig. 6B, this decrease in peak amplitude could be fitted to an exponential decay curve. Unlike the type I EPSPs, no apparent latency change was observed for type II EPSPs at any interstimulus interval (Fig. 6C).

In some cases (\( n = 7 \)), an apparent mixture of type I and II EPSPs was observed. With increasing stimulation currents, the amplitude of these “mixed” EPSPs increased gradually until a

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**FIG. 2.** Type I EPSPs show frequency-dependent facilitation. A: shown are the 1st 5 EPSPs, recorded in a lateral posterior nucleus neuron at resting membrane potential of −56 mV, in response to a 20-pulse train applied to corticothalamic fibers at stimulation frequencies ranging from 0.5 to 20 Hz. B: the graph illustrates the change in peak amplitude of the 20 EPSPs elicited by the stimulus train at various frequencies. C: the graph illustrates a gradual change in EPSP peak amplitude and a change in EPSP latency, with increasing stimulus intensity, recorded from the same cell illustrated in A and B.

**FIG. 3.** Type II EPSPs show frequency-dependent depression. A: shown are the 1st 5 EPSPs, recorded in a lateral posterior nucleus neuron at resting membrane potential of −60 mV, in response to a 20-pulse train applied to corticothalamic fibers at stimulation frequencies ranging from 0.5 to 20 Hz. B: the graph illustrates the change in peak amplitude of the 20 EPSPs elicited by the stimulus train at various frequencies. C: the graph illustrates an all-or-none change in EPSP peak amplitude and a relatively constant EPSP latency, with increasing stimulus intensity recorded from the same cell illustrated in A and B.
threshold was reached to induce a large amplitude EPSP (Fig. 7, A and B). A corresponding decrease in EPSP latency (from 4.2 ± 0.4 to 1.9 ± 0.6 ms, n = 7) was also observed as the stimulation current was increased (1 example is shown in Fig. 7B). Using stimulation currents smaller than the threshold for the large-amplitude EPSP, the response was similar to type I EPSPs in that paired-pulse stimulation induced an enhancement of the second response (Fig. 7C). A decrease in the EPSP latency was also observed as the interstimulus interval was decreased (Fig. 7E). In contrast, if stimulation currents large enough to elicit the large-amplitude EPSP of a mixed response were used, paired-pulse stimulation induced a decrease in the amplitude of the early component of the second response (Fig. 7F, G, and H), and no apparent latency shift was observed (Fig. 7E). This response was more similar to the type II EPSP. However, the amplitude of the late component of the second response was increased, which could be due to the presence of type I EPSPs. Thus we suggest that the mixed EPSPs result from a combination of type I and II EPSPs.

Figure 1B shows the distribution of cells in the LPN in which we recorded EPSPs after stimulation of the corticothalamic axons. Cells with type I EPSPs (white dots, n = 37) were located throughout the rostral LPN but were mainly located in the dorsal regions. Cells with type II EPSPs (red dots, n = 6) were located in the rostromedial region, and cells with mixed EPSPs (yellow dots, n = 5) were located in rostral LPN. These responses are consistent with the distribution of small type I and large type II corticothalamic terminals that we observed after injections of BDA in cortical area 17 (Fig. 1A).

Pharmacology of corticothalamic projections

We next investigated the involvement of NMDA and AMPA/kainate glutamate receptors in corticothalamic synaptic transmission and their role in paired-pulse enhancement of type I EPSPs. As previously reported for corticogeniculate and retinogeniculate projections (Chen et al. 2002; Granseth and Lindström 2003; Granseth et al. 2002; Lindström and Wrobel 1990; Turner and Salt 1998; von Krogh et al. 1999), corticothalamic projections to the LPN activate both NMDA and non-NMDA glutamate receptors. As illustrated in Fig. 8, in the presence of the NMDA receptor antagonist APV, the EPSP amplitude decreased, and the latency to the peak amplitude of the EPSP shifted from 8.9 ± 1.8 to 6.5 ± 0.7 ms (n = 6). This shift is likely due to the blockade of the late NMDA-mediated component of the EPSP (Scharfman et al. 1990). However, paired-pulse facilitation could still be elicited. In addition, the decrease in the latency of the second EPSP of the pair, observed after the shortest interstimulus intervals in control conditions, also occurred in the presence of APV (Fig. 8). As illustrated in Fig. 9, the AMPA/kainate glutamate receptor antagonist DNQX reduced the amplitude of the early component of corticothalamic EPSPs, and the latency to the peak amplitude of the EPSP shifted for both type I (8.5 ± 2.3 to 19.4 ± 2.4 ms, n = 6, Fig. 9A) and type II EPSPs (7.4 ± 1.6 to 16.4 ± 4.9 ms, n = 2, Fig. 9B). However, paired-pulse facilitation or depression was still observed in the presence of DNQX.

DISCUSSION

The main conclusion of this study is that two distinct types of EPSP could be evoked in the LPN neurons after stimulation of corticothalamic fibers. Corticothalamic EPSPs were mediated by both NMDA and non-NMDA glutamate receptors but differed in their latency to onset, amplitude, rising time, and responses to changes in stimulus intensity. The two types of EPSP also displayed different frequency-dependent changes. Paired-pulse stimulation paradigms elicited a facilitation of type I responses and a depression of type II responses. These differences are consistent with the innervation of the LPN by two different morphological types of corticothalamic terminals. As discussed in the following text, the features of type I and II EPSPs are highly correlated with the morphological features of corticothalamic terminals that originate from layers VI and V, respectively. However, future studies will be required to provide definitive proof of this correlation.

We consider the recorded EPSPs to specifically arise from activation of corticothalamic fibers for the following reasons. First, the stimulus pulses (considering the combined current intensity and pulse duration) are comparable to those used in previous studies of corticothalamic and retinogeniculate responses (Castro-Alamancos and Calcagnotto 2001; Turner and Salt 1998). Second, type II responses (or antidromic responses), could only be evoked by one of the four stimulating electrodes, indicating that each electrode activated a small number of
axons. In addition, in some cases, type I and II responses could be evoked in the same cell by different stimulation electrodes. Finally, the location of our stimulation electrodes was based on our anatomical observations regarding the trajectory of corticothalamic axons that innervate the LPN.

Type I response

Type I EPSPs exhibited a long latency, slow rise time, and a gradual increase in amplitude in response to increases in stimulus intensity. These properties are similar to those recorded in thalamic regions innervated by layer VI corticothalamic terminals such as the dLGN (Lindström and Wróbel 1990; Scharfman et al. 1990; Turner and Salt 1998; von Krosgik et al. 1999) ventrobasal nucleus (Castro-Alamancos and Calcagnotto 2001; Kao and Coulter 1997), and medial geniculate nucleus (Bartlett and Smith 2002). In these nuclei, layer VI corticothalamic terminals are known to be small profiles that contain densely packed round vesicles (RS profiles) and contact small caliber dendrites. In fact, the majority of corticothalamic terminals in the LPN (and other higher-order nuclei) (Wang et al. 2002) are RS profiles (Li et al. 2003b); this may help explain why we encountered far more type I responses than type II.

The morphology of layer VI corticothalamic axons also correlates well with the long latency of the type I EPSPs and the graded increases in EPSP amplitude with increased stimulation intensity. In all nuclei studied, corticothalamic axons that
originate from layer VI are of extremely fine caliber (Rouiller and Welker 2000) and have slow conduction velocities. Additionally, layer VI corticothalamic terminals primarily target the distal dendrites of thalamocortical cells (Erisir et al. 1997; Jones and Powell 1969; Li et al. 2003b; Vidnyánszky and Hámori 1994). Thus, the latencies of EPSPs recorded at the soma should be longer for those arising from layer VI corticothalamic terminals than for those arising from the layer V corticothalamic terminals, which contact more proximal dendrites (Feig and Harting 1998; Li et al. 2003b; Vidnyánszky et al. 1996).

Layer VI axons give rise to numerous small boutons (Bourassa and Deschenes 1995; Murphy and Sillito 1996; Murphy et al. 2000). Presumably, increasing stimulus intensity recruits the release of glutamate from increasing numbers of layer VI axons and/or boutons per axon. Because LPN and dLGN dendrites are contacted by multiple RS profiles, each neuron is likely to receive input from multiple layer VI axons; this would be reflected in graded increases in EPSP amplitude after increases in stimulation intensity. This would also explain why in some cases we were able to evoke type I responses, in single neurons, from more than one of the four stimulating electrodes. This might also explain why type I EPSPs were generally evoked using lower stimulation currents than were type II EPSPs. Our stimulation electrodes were much more likely to be in close proximity to the numerous layer VI corticothalamic axons than the sparse layer V corticothalamic axons (although on occasion type II EPSPs were evoked with small currents, suggesting that on occasion our stimulation electrodes were located close to layer V corticothalamic axons).

The innervation of thalamic neurons by multiple layer VI axons may also contribute to the paired-pulse facilitation. Increases in stimulation frequency may increase the probability of glutamate release from synaptic vesicles in increased numbers of terminals (Dittman et al. 2000; Granseth and Lindström 2003). It has been proposed that synaptic facilitation may result from increased presynaptic calcium concentrations (Zucker 1999). Growth-associated protein 43, a presynaptic protein found exclusively within RS profiles in the visual thalamus (Bickford 1999), has also been implicated in activity-dependent neurotransmitter release (Dekker et al. 1989; Fischer von Mollard et al. 1991).

Finally, we observed a decrease in the latency of type I
corticothalamic EPSPs after paired-pulse stimulation. This phenomenon has also been reported for corticothalamic axons (Beierlein and Connors 2002). It has been suggested that latency decreases are the result of a period of supernormal conduction velocity after axon activation. Such a supernormal period has been described for layer VI corticogeniculate axons (Kelly et al. 2001; Swadlow and Waxman 1975; Swadlow et al. 1980). Alternatively, the decrease in the latency of type I corticothalamic EPSPs after paired-pulse stimulation may reflect the recruitment of additional corticothalamic axons by increasing their excitability. Indeed, we observed a latency shift for type I EPSPs at the highest stimulation currents (Fig. 2C).

**Type II response**

Type II EPSPs exhibited a short latency, fast rise time, and an all-or-none amplitude change in response to increasing stimulus intensity. In the visual cortex, it has been reported that the axonal conduction velocities of layer V corticocortical neu-
rons are much faster than those of layer VI corticogeniculate neurons. Because layer V corticotectal axons and layer VI corticogeniculate axons branch to innervate the LPN (Bourassa and Deschenes 1995), this difference in axonal conduction velocities corresponds well with the difference in EPSP latencies exhibited by type I and II EPSPs. Furthermore, layer V corticothalamic terminals originate from large-diameter axons whose myelin sheaths extend to and may even surround syn-

**FIG. 8.** Corticothalamic EPSPs activate NMDA receptors. In the presence of the NMDA glutamate receptor antagonist 2-amino-5-phosphonovalerate (APV), there was a decrease in the amplitude of a type I EPSP. However, paired-pulse facilitation (1st EPSP gray, 2nd EPSP black), as well as a decrease in the latency of the 2nd EPSP, were still observed.

**FIG. 9.** Corticothalamic EPSPs activate non-NMDA receptors. In the presence of the AMPA/kainate glutamate receptor antagonist DNQX, there was a decrease in the amplitude of type I (A) and type II (B) EPSPs. However, paired-pulse facilitation (A) or depression (B) were still observed (1st EPSP gray, 2nd EPSP black).
aptic connections within the LPN (Li et al. 2003b). Thus it is not surprising that even for the short segments of axons stimulated in our in vitro preparation, a shorter latency could be detected for type II EPSPs when compared with type I EPSPs. In addition, as mentioned in the preceding text, layer VI corticothalamic axons give rise to large numbers of small boutons. This contrasts with the layer V corticothalamic axons, which terminate in relatively restricted regions with small clusters of large boutons. Thus stimulation of layer V axons is more likely to result in the all-or-none release of glutamate from a single cluster of terminals. This would also explain why we were able to evoke type II responses, in single neurons, from only one of the four stimulating electrodes.

The morphology of layer V corticothalamic terminals and the characteristics of type II EPSPs closely resemble the morphology of retinogeniculate terminals and the characteristics of retinogeniculate EPSPs. Both types of terminals are large profiles that contain round vesicles (RL profiles) that contact large-caliber dendrites of thalamocortical cells in complex synaptic arrangements known as glomeruli. Similar to type II corticothalamic EPSPs, retinogeniculate or lemniscal EPSPs exhibit short latencies, fast rise times, all-or-none amplitude increases in response to increased stimulus intensity, and depressed responses to repetitive stimulation (Bartlett and Smith 2002; Castro-Alamancos 2002; Turner and Salt 1998).

Synaptic depression may result from either presynaptic decreases in neurotransmitter release (King et al. 2001; Zucker 1999) or postsynaptic mechanisms such as receptor desensitization (Chen et al. 2002; Keilland and Heggelund 2002). However, anatomical observations suggest the possibility of a presynaptic origin. For example, the unique characteristics of RL profiles and their synaptic arrangements, which appear to be isolated from the surrounding neuropil, provide a potential means to decrease the influx of calcium ions during repetitive stimulation (King et al. 2001). The low packing density of synaptic vesicles contained within RL profiles may also contribute to EPSP depression. In contrast to RS profiles, which are densely packed with synaptic vesicles, the vesicles in RL profiles are more scattered (Li et al. 2003b). Thus repetitive stimulation may cause a depletion of release-ready vesicles (Granseth et al. 2002; Zucker 1999) in RL profiles that does not occur in the vesicle rich RS profiles.

Interestingly, EPSPs elicited by stimulation of thalamocortical terminals, which are the largest terminal boutons in layer IV (A. Erisir, personal communication), also display paired-pulse depression (Chung et al. 2002; Gil et al. 1999; Stratford et al. 1996). In addition, in the cerebellum large climbing fiber terminals display paired-pulse depression while smaller parallel fiber terminals are facilitated (Ku-Friedman et al. 2001). These studies suggest that terminal morphology is highly correlated with short term synaptic plasticity.

Functional implications

Two recent theories have sought to elucidate the organization of the dorsal thalamus. First, it has been proposed that inputs can be defined as “drivers” or “modulators” (Crick and Koch 1998; Sherman and Guillery 1998). For example, retinogeniculate terminals are considered drivers because the response properties of cells in the dLGn are very similar to the retinal ganglion cells that innervate them (Cleland et al. 1971).

In contrast, corticogeniculate terminals are considered modulators because they elicit more subtle effects (Geisert et al. 1981; Kalil and Chase 1970; Richard et al. 1975). The second idea divides thalamic nuclei into two types on the basis of the origin of their driving input (Guillery 1995). “First-order” nuclei, such as the dLGn, are driven by relatively direct sensory input and modulated by layer VI cortical input. In contrast, “higher-order” nuclei are driven by cortical layer V and modulated by cortical layer VI. Our results suggest that the EPSPs elicited by stimulation of layer V corticothalamic terminals are very similar to those elicited by stimulation of retinogeniculate terminals. Thus in terms of their effects on the membrane potential of postsynaptic neurons, layer V corticothalamic terminals can be considered equivalent to direct sensory inputs.

Several models have suggested that synaptic depression is important for signal differentiation and sensitivity (Abbott et al. 1997; Cook et al. 2003). Compared with the necessity of precision in the detection of primary sensory afferents, the need for precision in layer V corticothalamic inputs is less obvious. In the visual cortex, layer V corticocortical cells have very large receptive fields and respond to high velocity moving stimuli with little sensitivity to stimulus orientation or direction (Lemmon and Pearlman 1981; Mangini and Pearlman 1980). Because corticocortical cells branch to innervate the LPN (Bourassa and Deschénes 1995), it is likely that type II corticothalamic EPSPs do not transmit precise visual features, but signal the movement of objects entering the visual field.

Given the proposed functions of the pulvinar and lateral posterior nuclei in directing visual attention, perhaps the layer V inputs are important for the rapid activation of the LPN following the appearance of novel signals. In turn, the LPN’s projections to cortical layer I (Abramson and Chalupa 1985) may be important for activating and synchronizing the activity of multiple cortical areas, a process thought to be important for attention and perception (Crick and Koch 1990; Niebur et al. 1993; Olshausen et al. 1993).

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DISCLOSURES

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