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DYNAMIC PROPERTIES OF CORTICOTHALAMIC EXCITATORY POSTSYNAPTIC POTENTIALS AND THALAMIC RETICULAR INHIBITORY POSTSYNAPTIC POTENTIALS IN THALAMOCORTICAL NEURONS OF THE GUINEA-PIG DORSAL LATERAL GENICULATE NUCLEUS

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Abstract—The properties of postsynaptic potentials evoked by stimulation of cortical, retinal and GABAergic thalamic afferents were examined *in vitro* in thalamocortical neurons of the guinea-pig dorsal lateral geniculate nucleus. Brief trains of stimulation (2–10 stimuli) delivered to corticothalamic fibers led to a frequency-dependent increase in excitatory postsynaptic potential amplitude associated with an increase in activation of both *N*-methyl-D-aspartate and non-*N*-methyl-D-aspartate glutamate receptors. In addition, repetitive stimulation of corticothalamic fibers also gave rise to a slow excitatory postsynaptic potential that was blocked by local application of the glutamate metabotropic receptor antagonist α-methyl-4-carboxyphenylglycine. In contrast, repetitive stimulation of optic tract fibers resulted in monosynaptic excitatory postsynaptic potentials that did not potentiate and were not followed by the generation of a slow excitatory postsynaptic potential.

Repetitive activation of the optic radiation also evoked both $GABA_A$ and $GABA_B$ receptor-mediated inhibitory postsynaptic potentials. These inhibitory postsynaptic potentials exhibited frequency-dependent depression during repetitive activation. The presence of frequency-dependent facilitation of corticothalamic excitatory postsynaptic potentials and frequency-dependent decrement of inhibitory postsynaptic potentials, as well as the ability of corticothalamic fibers to activate glutamate metabotropic receptors, suggests that sustained activation of corticothalamic afferents *in vivo* may result in postsynaptic responses in thalamocortical cells that are initially dominated by GABAergic inhibitory postsynaptic potentials followed by prominent monosynaptic excitatory postsynaptic potentials as well as a slow depolarization of the membrane potential.Therefore, the corticothalamic system may inhibit or enhance the excitability and responsiveness of thalamocortical neurons, based both on the spatial and temporal features of thalamocortical interactions. © 1999 IBRO. Published by Elsevier Science Ltd.

Key words: facilitation, depression, metabotropic glutamate receptor.

The processing and transmission of visual information through the dorsal lateral geniculate nucleus (LGNd) is under the influence of many different aspects of the neuronal circuit in which these cells are embedded, including the electrophysiological properties of each cell type, the properties of synapses and synaptic networks, as well as the status of various modulatory neurotransmitters (reviewed in Refs 31, 49 and 52). One prominent feature of the dorsal lateral geniculate nucleus, and indeed the thalamus in general, is the presence of a massive axonal innervation arising from layer VI pyramidal cells in the cerebral cortex (reviewed in Refs 22 and 49). These axons densely innervate thalamocortical neurons in all layers of the LGNd as well as GABAergic neurons, both local and in the thalamic reticular nucleus.[35,45,46]

Previous electrophysiological investigations of the corticothalamic pathway have demonstrated that these axons exhibit a strong monosynaptic excitatory influence on thalamocortical, thalamic reticular, and local GABAergic interneurons.[1,2,10,24,26] The ability of corticothalamic inputs to strongly activate GABAergic neurons within the thalamus also results in the generation of robust di-synaptic inhibitory postsynaptic potentials (IPSPs) in thalamocortical

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Abbreviations: 1S,3R-ACPD, 1S,3R-1-amino-1,3-cyclopentanedicarboxylic acid; ACSF, artificial cerebrospinal fluid; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionate; APV, 2-amino-5-phosphonovaleric acid; CNQX, 6-cyano-7-nitroquinoxilane-2,3-dione; EPSP, excitatory postsynaptic potential; IPSP, inhibitory postsynaptic potential; LGNd, dorsal lateral geniculate; α-MCPG, (±) α-methyl-4-carboxyphenylglycine; NRT, thalamic reticular nucleus; OT, optic tract; PGN, perigeniculate nucleus.

cells, giving the corticothalamic system the ability to either directly excite, or indirectly inhibit, the output of the thalamus.

Previously it has been suggested that the spatial organization of excitatory and inhibitory connections may be important in determining whether or not the cortex exerts an overall excitatory or inhibitory influence on thalamocortical activity.[37,56] For example, the experiments of Tsumoto *et al.*[56] demonstrated with cross-correlation techniques that activity in cortical neurons may be followed by either excitatory or inhibitory influences in cells of the LGNd. Another important variable in determining the influence of the descending corticothalamic influence is the temporal pattern of activation of these fibers and the effects of this on excitatory and inhibitory neurotransmission. Repetitive activation of the corticothalamic pathway results in a marked frequency-dependent facilitation in the excitatory influence,[10,24,26] as well as the generation of a slow excitatory postsynaptic potential (EPSP) that follows the monosynaptic fast EPSPs and that may be several seconds in duration.[34] In other neuronal systems, frequency-dependent facilitation has been demonstrated to result from both increases in transmitter release by the excitatory terminals (reviewed in Refs 15, 28 and 62) as well as decreases in the release of GABA from di-synaptically activated inhibitory neurons.[8,9,40] Indeed, dual intracellular recordings from pairs of GABAergic perigeniculate and thalamocortical neurons have revealed that repetitive activation of perigeniculate nucleus (PGN) to thalamocortical GABAergic synapses results in frequency-dependent depression.[25a]

In hippocampal pyramidal cells, frequency-dependent depression of GABAergic transmission has been demonstrated to result from the activation of presynaptic $GABA_B$ receptors through the release of GABA itself (reviewed in Ref. 54). Present evidence suggests that this presynaptic action of GABA may arise through inhibition of Ca^{2+} currents in the presynaptic membrane.[27,61] Similarly, in the mammalian thalamus the activation of $GABA_B$ receptors also potently inhibits the function of GABAergic terminals, apparently through a presynaptic mechanism.[47,57]

The generation of a prolonged slow EPSP following the repetitive activation of corticothalamic fibers has important functional consequences for the influence of this pathway on the generation of thalamocortical activity. Thalamocortical neurons depolarize by 10–20 mV in the transition from slow wave sleep to waking or rapid eye movement sleep.[20] Previous investigations have suggested that the activation of brainstem and hypothalamic systems may underlie this depolarization of thalamocortical neurons (reviewed in Refs 31, 51 and 52). However, the ability of the activation of corticothalamic fibers to generate a slow EPSP that is identical to that associated with activation of these brainstem inputs suggests that the activation of the corticothalamic pathway may also underlie the depolarization of thalamocortical cells with arousal.[34] Previously, we have suggested that the corticothalamic slow EPSP may be mediated through the activation of glutamate metabotropic receptors, since the activation of these receptors with a selective agonist generated a similar response[34] and the corticothalamic pathway is believed be at least in part glutamatergic.[34] However, pharmacological examination of this possibility with antagonists to glutamate metabotropic receptors remained to be performed. Portions of this work have appeared in abstract form.[59]

EXPERIMENTAL PROCEDURES

Male and female guinea-pigs (Hartley; $n = 56$) were deeply anaesthetized with sodium pentobarbital (35 mg/kg i.p.) and killed by decapitation, as previously described.[32,33] The thalamus was rapidly dissected and was then sectioned parasagittally at 400 μm in the plane of either the corticothalamic or the optic tract fibers using a Vibratome (Pelco). Slices were maintained in an interface chamber (Fine Science Tools) at $35.5 \pm 1°C$ and bathed with an artificial cerebrospinal fluid solution (ACSF) containing 126 mM NaCl, 2.5 mM KCl, 1.2 or 2 mM $MgSO_4$, 26 mM $NaHCO_3$, 1.25 mM NaH_2PO_4, 2 mM $CaCl_2$ and 10 mM glucose, saturated with 95% O_2/5% CO_2 to a final pH of 7.4. Pharmacological antagonists were applied either in the bathing medium or locally with the "pico-drop" method in volumes of 5–20 pl. The glutamate receptor antagonists D- or DL-2-amino-5-phosphonovaleric acid (APV, 25–50 μM; Sigma) and 6-cyano-7-nitroquinoxilane-2,3-dione (CNQX, 10–25 μM; Research Biochemicals) were used to block, respectively, *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors. GABA receptor antagonists bicuculline methiodide (30–500 μM, Research Biochemicals), picrotoxin (100 μM) and 2-Hydroxysaclofen (0.5–2 mM, Research Biochemicals) were used to block $GABA_A$ or $GABA_B$ receptors, respectively.

Electrical stimulation (10–400 μA, 50–100 μs duration) was generated using a constant current generator (World Precision Instruments) and passed through a concentric bipolar stimulating electrode placed in either the corticothalamic or optic tracts. The stimulus trains were generated using a multichannel programmable pulse generator (Master-8, A.M.P.I.). No effort was made to remove the thalamic reticular nucleus (NRT) from the slice preparation.

Intracellular recording microelectrodes were made from thin-walled glass capillary tubes (1 mm o.d., 0.67 mm o.d., World Precision Instruments) and pulled on a Brown-Flaming micropipette puller (Sutter Instruments). The micropipettes were filled with either 4 M potassium acetate or 4 M potassium acetate and 50 mM lidocaine N-ethyl bromide quarternary salt (QX-314, Research Biochemicals Inc.), and had final tip resistances of 40–65 MΩ. Intracellular recordings were performed using an Axoclamp-2A amplifier (Axon Instruments).

The use of QX-314

QX-314 is a quaternary derivative of lidocaine bromide salt which blocks voltage-dependent sodium channels when included in the intracellular recording electrode solution.[39] In experiments without QX-314, EPSPs activated action potentials at depolarized potentials and low-threshold Ca^{2+} spikes and bursts of action potentials at more hyperpolarized membrane potentials. Therefore to examine facilitation of EPSPs without the confounding influence of the

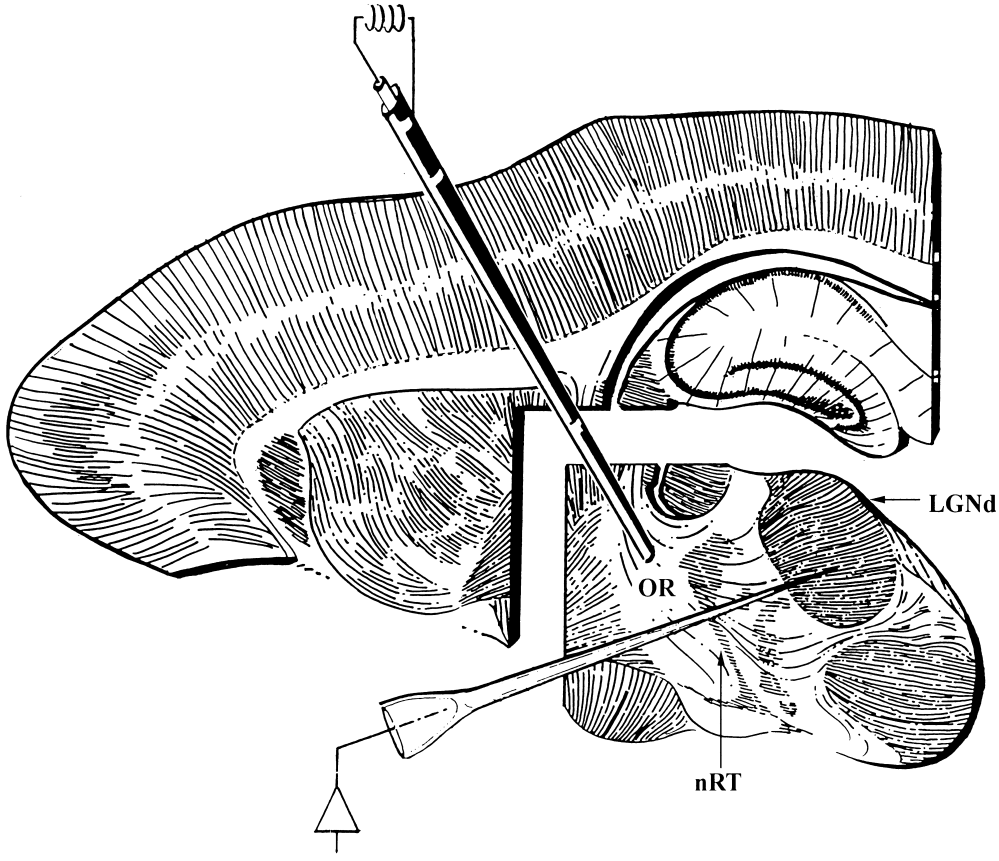

Fig. 1. A schematic summary diagram illustrating the parasagittal orientation of the thalamus and dorsal lateral geniculate (LGNd) used in this study. The stimulating electrode is located in the cortical white matter and was located at least 1–2 mm outside of the LGNd. Figure drawn by Thierry Bal.

activation of Na^+ and low-threshold Ca^{2+} channels, we routinely included QX-314 in the recording micropipette and depolarized the thalamocortical cells with the intracellular injection of current to membrane potentials where the low threshold Ca^{2+} current is inactivated (i.e. positive to -65 mV). QX-314 was allowed to diffuse into the cell with either no holding current or with a slight depolarizing current (0.1–0.5 nA). The effective block by QX-314 took place over a period of 10–20 min and was judged to have occurred when an action potential could not be elicited by depolarizing current injections, in response to EPSPs evoked by corticothalamic stimulation, or upon activation of a rebound low threshold Ca^{2+} spike through the injection of a hyperpolarizing current pulse. In addition to blocking the voltage-dependent sodium channels, QX-314 also prevents $GABA_B$ receptor activation of potassium currents in the recorded cell.[39]

Isolation and stimulation of fiber tracts

The path taken by corticothalamic fibers between the visual cortex and the LGNd has been described in detail in both rat[60] and cat.[45,46] The course of the guinea-pig corticothalamic projection from the primary visual cortex to the LGNd was determined here using biocytin as an anterograde tract tracer.[21] From these tracing experiments it was determined that the corticothalamic fibers coursed anteriorally and then in a posterior and lateral direction from the visual cortex to the LGNd. Owing to a dominant anterior to posterior direction at the level of the thalamus, parasagittal sections were determined to be the optimal plane for the formation of geniculate slices for stimulation of corticothalamic fibers.

Sections in which the optic tract (OT) was stimulated were cut parallel to the plane of the OT as it travels along the ventrolateral and lateral margin of the diencephalon. Stimulation of the OT was made at least 1 mm outside the lateral geniculate whereas stimulation of the corticothalamic fibers was made 1–2 mm anterior to the border of the LGNd (see Fig. 1). Stimulus intensity was typically set at one and a half to twice the threshold required to resolve an EPSP in the second or third stimulus in a train of five stimuli. The stimulus intensity ranged from 60–400 μA for the activation of corticothalamic afferents within the optic radiation and 10–100 μA for the activation of OT axons. Increasing stimulus intensity above threshold lead to a progressive increase in amplitude of the evoked corticothalamic EPSP, whereas increasing stimulus intensity in the OT led to clear "jumps" in EPSP amplitude, presumably corresponding to the activation of individual fibers within the optic tract.[42]

RESULTS

Optic radiation stimulation evokes both excitatory and inhibitory postsynaptic potentials

Intracellular recordings were obtained from 60 thalamocortical neurons in the LGNd. A representative sample of 15 of these cells exhibited an average input resistance of 69 ± 12 MΩ, resting membrane potential of -65 mV (± 3.3 mV) and were capable

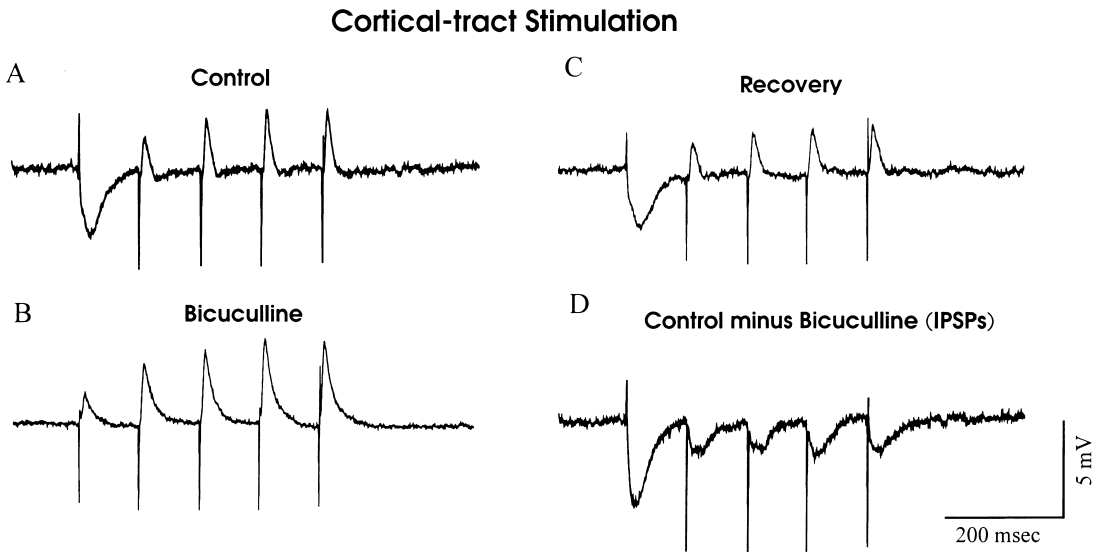

Fig. 2. Repetitive stimulation of optic radiation evokes both EPSPs and IPSPs (A; Control). Application of the $GABA_A$ receptor antagonist bicuculline methiodide (B; 50–100 μM; Bicuculline) reversibly (C; Recovery) blocks IPSP activity and reveals that corticothalamic EPSPs are facilitated by repetitive stimulation. The difference between the control and the bicuculline conditions reveals that evoked IPSPs undergo depression during repeated activation (D; Control minus bicuculline). In these experiments action potentials and postsynaptic $GABA_B$ IPSPs were prevented by including 50 mM QX-314 in the recording electrode. Membrane potentials were -53 ± 2 mV.

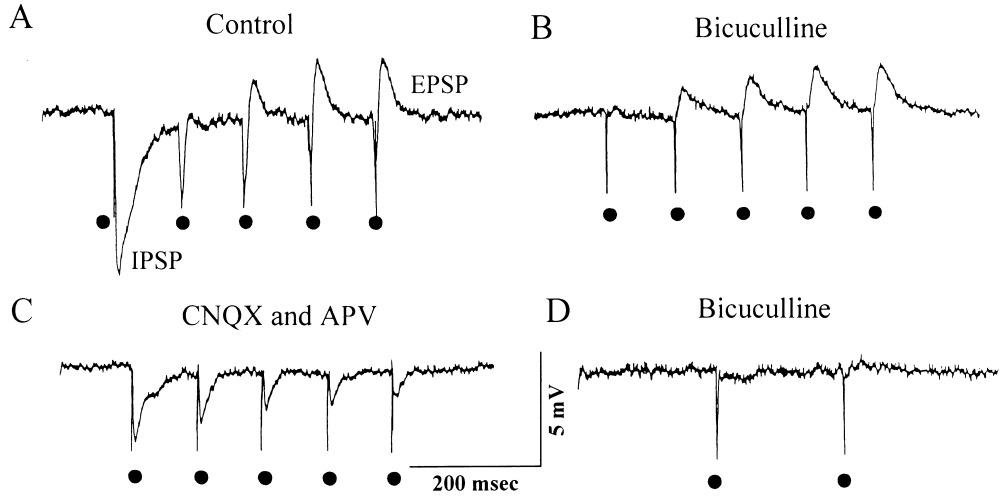

Fig. 3. Repetitive activation modulates the amplitude of both EPSPs and IPSPs. As in the previous figure repeated activation of the optic radiation or the corticothalamic white matter evoked both EPSPs and IPSPs (A, Control). Application of bicuculline methiodide (50–100 μM) blocked the IPSPs. The isolated corticothalamic EPSPs were facilitated during repeated activation. Thus, corticothalamic EPSP facilitation does not require the modulation of IPSPs (B, Bicuculline). After washout of bicuculline methiodide, application of glutamate antagonists CNQX (20 μM) and APV (20 μM) blocked the evoked corticothalamic EPSPs. Isolated $GABA_A$ IPSPs were depressed by repeated activation (C, CNQX and APV). These IPSPs were abolished by the local application of the $GABA_A$ antagonist bicuculline (500 μM in the micropipette; D). Membrane potential was -54 ± 1 mV and the recording electrode contained 50 mM QX-314.

of generating repetitive trains of action potentials upon depolarization.

Repetitive stimulation at 10 Hz of fibers lying in the optic radiation approximately 0.5 to 2 mm anterior to the LGNd (see Fig. 1) resulted in both IPSPs and EPSPs in thalamocortical neurons in normal bathing solution and recorded with microelectrodes containing either 4 M potassium acetate or 50 mM QX-314 dissolved in 4 M potassium acetate (Figs 2A and 3A). Initially, the evoked postsynaptic responses were dominated by the presence of a large IPSP, although this quickly gave way to prominent EPSPs during the stimulus train (Figs 2A and Fig. 3A). The EPSPs presumably arise from the

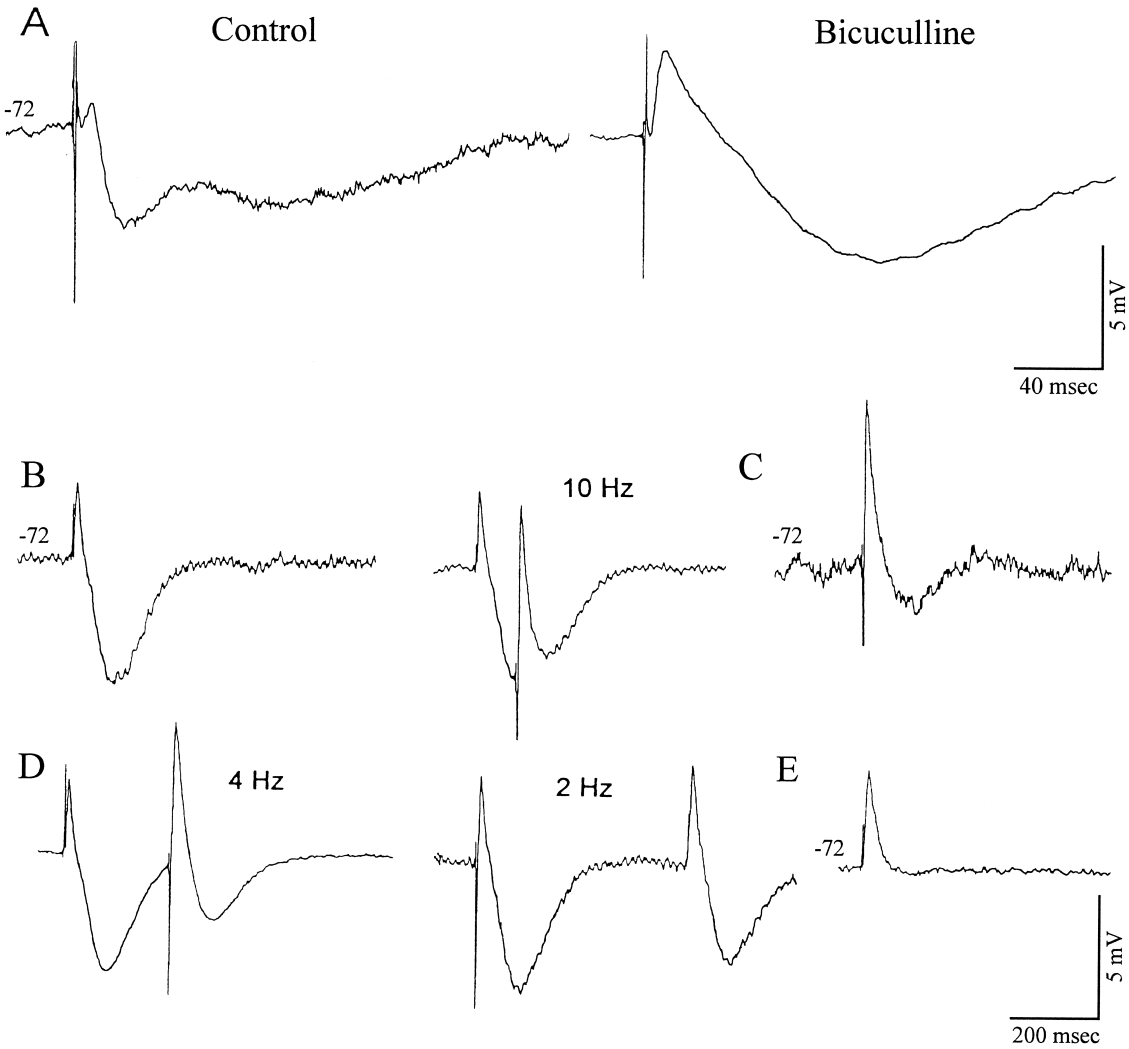

Fig. 4. $GABA_B$ receptor-mediated IPSPs exhibit depression. Stimulation of the optic radiation evokes both EPSPs and IPSPs (Control A,B). At higher temporal resolution the IPSPs appear biphasic (Control, A). Application of the $GABA_A$ antagonist bicuculline methiodide abolished the early component of the IPSP (A, Bicuculline) but did not diminish the slower second component of the IPSP. (B) The slow, bicuculline resistant, IPSPs showed frequency-dependent depression. Comparison of the second of the two evoked IPSPs with either the first IPSP or a single IPSP (first trace in B) demonstrates that the slow IPSP is depressed by repeated activation. (C) The subtraction of a 10 Hz paired IPSP from a single IPSP (first trace in B) also demonstrates prominent depression. (D) The depression at 10 Hz was greater than that observed at the lower stimulation rates of 2 and 4 Hz. (E) With bicuculline present, the local application of the $GABA_B$ antagonist 2-hydroxysaclofen (1 mM) abolished the slow IPSP. Thus the slower second component of the IPSP is mediated by $GABA_B$ receptor activation. Recordings were made with 4 M potassium acetate in the recording electrodes. The resting membrane potentials were -72 ± 1 mV (A–E). Bicuculline methiodide was present for all except A, control.

activation of corticothalamic fibers that form monosynaptic connections with the intracellularly recorded thalamocortical cell, while the IPSPs may arise from either the activation of neurons or axons of the thalamic reticular nucleus that innervate the recorded neuron or through the excitation of local GABAergic LGNd interneurons owing to the activation of the corticothalamic input.

The changes in amplitude and time-course of the evoked IPSPs and EPSPs occurring during the response to the stimulus train suggested that there was both a frequency-dependent decrease in IPSP amplitude and a frequency-dependent increase in corticothalamic EPSP amplitude (Fig. 2, control). The following experiments were performed to examine this hypothesis.

Optic radiation-evoked excitatory postsynaptic potentials strongly facilitate in the absence of inhibitory postsynaptic potentials

The block of $GABA_A$ and $GABA_B$ receptors revealed isolated EPSPs in response to stimulation of the optic radiation (Fig. 2B, bicuculline). $GABA_A$

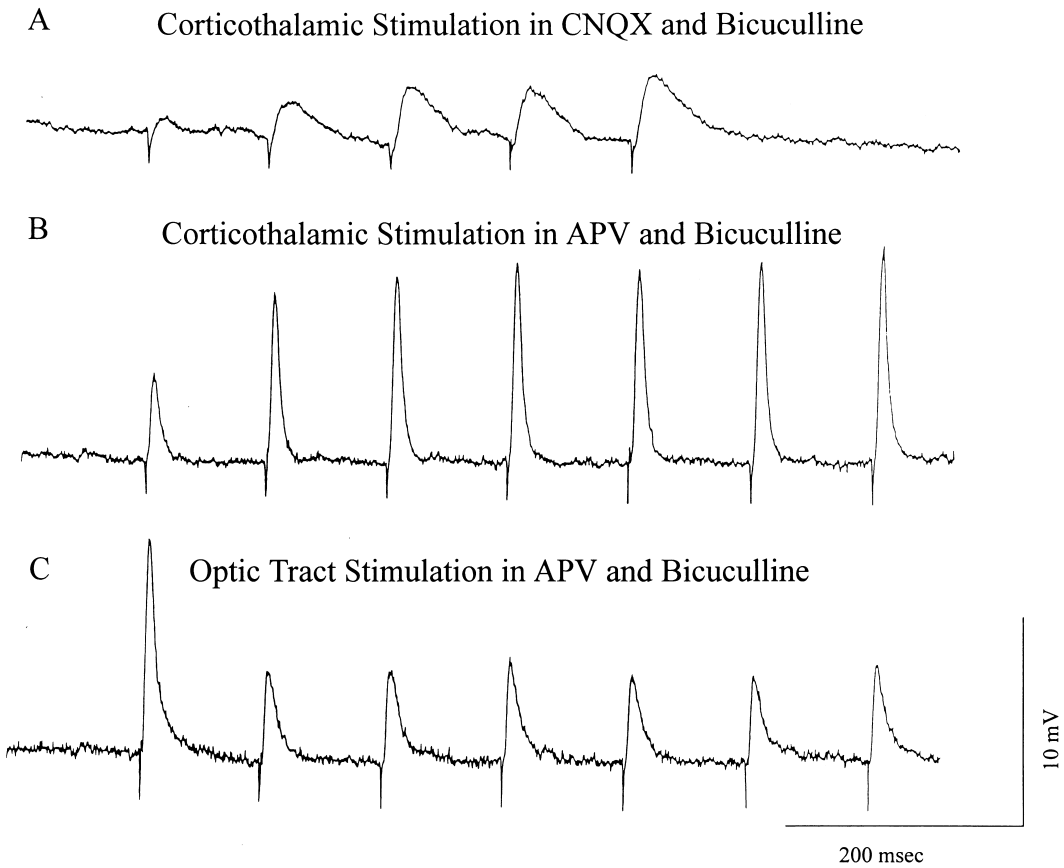

Fig. 5. Repetitive activation of the corticothalamic fibers revealed that both NMDA (A) and non-NMDA (B) receptors mediate frequency-dependent facilitation. In contrast, optic tract-evoked EPSPs undergo depression in response to repetitive activation (C). EPSPs were isolated from IPSPs by including 50 mM QX-314 in the recording electrode and bicuculline methiodide (50–100 μM) in the ACSF. (A) NMDA EPSPs were isolated by including CNQX (12–25 μM) in the bathing medium and excluding Mg^{2+}. These NMDA receptor-mediated EPSPs exhibited marked frequency-dependent facilitation. (B). Isolation of AMPA/kainate receptor-mediated EPSPs by including APV (100–500 μM) and bicuculline (50–100 μM) in the bathing medium. As with the NMDA receptor-mediated EPSPs, excitatory PSPs mediated by AMPA/kainate receptors also exhibit facilitation. (C) Repetitive stimulation of optic tract axons results in a decrease in EPSP amplitude between the first and second evoked responses, followed by a relatively maintained amplitude at this frequency. The membrane potentials were -61 ± 1 mV.

receptor-mediated IPSPs were blocked by either local (500 μM in micropipette) or bath (30–100 μM) application of the $GABA_A$ receptor antagonist bicuculline methiodide ($n = 46$). $GABA_B$ receptor-mediated IPSPs were blocked either through the inclusion of 50 mM QX-314 in the recording electrode (Fig. 2; $n = 35$) or through the bath application of 2-hydroxysaclofen (1–2 mM; $n = 10$). The EPSPs evoked by repetitive stimulation of the optic radiation (following the block of $GABA_A$ and $GABA_B$ receptor-mediated IPSPs) exhibited strong facilitation (80–500%; $n = 15$; Fig. 2B, bicuculline). Examining the difference between the postsynaptic responses before and after the local application of bicuculline revealed that the evoked IPSPs show marked depression during repetitive stimulation, particularly between the first and second IPSPs (Fig. 2D, Control minus bicuculline). In order to directly test this hypothesis, EPSPs were blocked with the application of CNQX (250 μM in micropipette; 12–25 μM in bath) and APV (100–500 μM in micropipette; 20–50 μM in bath; Fig. 3C). IPSPs, evoked in this circumstance (with direct electrical stimulation placed in the NRT anterior to the LGNd) exhibited marked depression (30–70%) during repetitive stimulation (Fig. 3C; $n = 21$). These IPSPs were mediated largely by $GABA_A$ receptors, since they were blocked by the local application of bicuculline (Fig. 3D).

The activation of corticothalamic fibers in normal solution could also result in the activation of fast EPSPs followed by both fast $GABA_A$ receptor and slow $GABA_B$ receptor-mediated IPSPs in neurons recorded with 3 M KAc-containing microelectrodes (Fig. 4A, control). Local application of bicuculline resulted in block of the fast component, resulting in an enhancement of both the fast EPSP and the slow IPSP (Fig. 4A, bicuculline).[7] Paired stimulation of

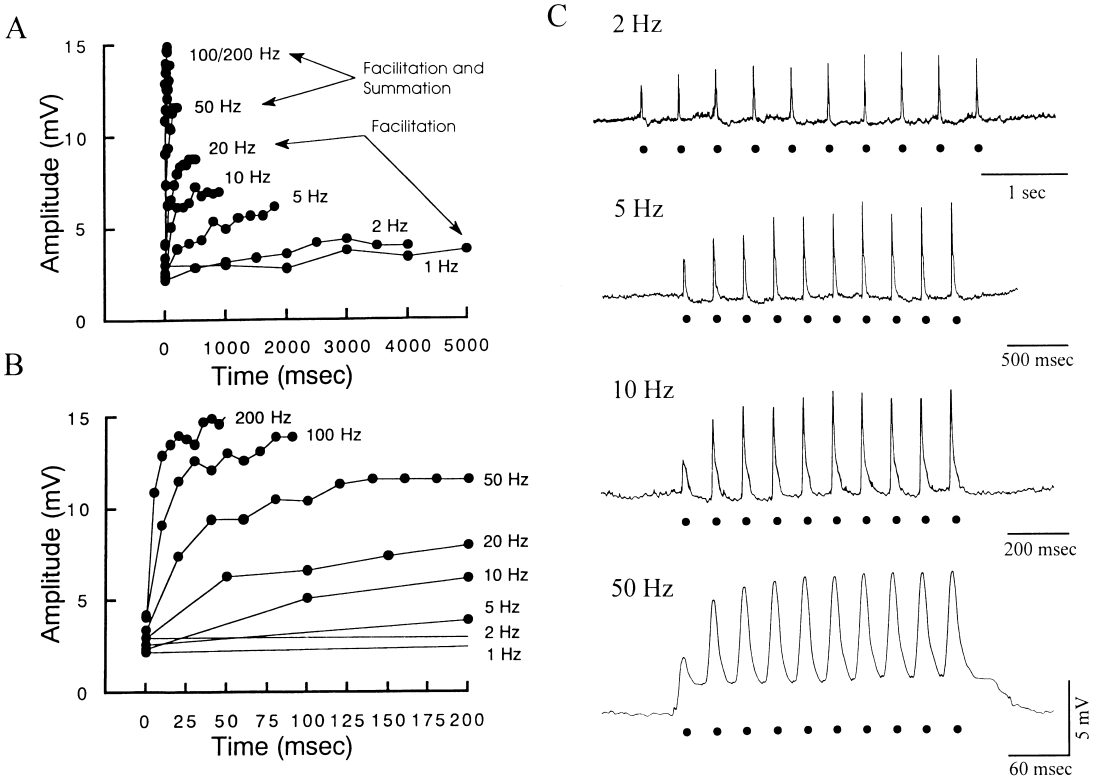

Fig. 6. Frequency dependence of facilitation and summation. Corticothalamic fibers were activated at different rates of stimulation (1–200 Hz). A, B and C show these different frequencies expanded at different time scales. Graphs A and B show that even at frequencies as low as 1 Hz corticothalamic EPSPs facilitate and this facilitation increases markedly with increases in the frequency of stimulation. At stimulation rates above 20 Hz both facilitation and temporal summation occur (C, 50 Hz). These EPSPs were isolated from IPSPs through the inclusion of QX-314 (50 mM) in the intracellular micropipette and the local application of bicuculline (0.5–1 mM in micropipette). Membrane potential for this cell was -56 ± 2 mV.

the corticothalamic inputs revealed a marked potentiation of the EPSP evoked by the second stimulus, and a decrement in the amplitude of the second slow IPSP, even if there was little or no overlap in the evoked PSP sequences (e.g., Fig. 4D, 2 and 4 Hz). Local application of the $GABA_B$ antagonist 2-hydroxysaclofen (1 mM in bath) blocked the bicuculline-insensitive IPSP (Fig. 4E), demonstrating that this event was a $GABA_B$ receptor-mediated IPSP.

Excitatory postsynaptic potentials mediated by either N-*methyl*-D-*aspartate or* α-*amino*-3-*hydroxy*-5-*methylisoxazole*-4-*proprionate/kainate glutamate receptors exhibit facilitation*

Repetitive stimulation of optic radiation fibers in the presence of the α-amino-3-hydroxy-5-methylisoxazole-4-proprionate (AMPA)/kainate receptor antagonist CNQX (25 μM) and following the removal of Mg^{2+} from the bathing medium (Fig. 5A; $n = 12$) revealed EPSPs, presumably mediated by NMDA receptors, that exhibited strong facilitation (66–290%). Similarly, repetitive activation of EPSPs by stimulation of the optic radiation following the bath application of the NMDA receptor antagonist D-APV/DL-APV (25–50 μM, $n = 18$; normal Mg^{2+}) also revealed EPSPs that exhibit marked facilitation (78–505%; Fig. 5B). Application of both CNQX and APV abolished these fast EPSPs (not shown; see Fig. 3C).

Repetitive stimulation of the OT in the presence of bicuculline resulted in EPSPs that did not exhibit facilitation, and in fact, typically exhibited a reduction in amplitude from the first to second EPSP (57–88%; Fig. 5C).[41] Similar results were obtained even when NMDA receptors were not blocked ($n = 4$). In normal bathing medium, stimulation of OT fibers resulted in typical EPSP–IPSP sequences (see Ref. 7). Repetitive stimulation of these fibers resulted in depression of both the EPSP and IPSP amplitude (not shown).

Frequency dependence and time-course of facilitation

The facilitation of isolated monosynaptic corticothalamic EPSPs is frequency dependent. The delivery of repetitive trains of 10 stimuli to the optic radiation at various frequencies revealed facilitation even at frequencies as low as 1 Hz ($n = 46$; Fig. 6). This facilitation increased markedly with

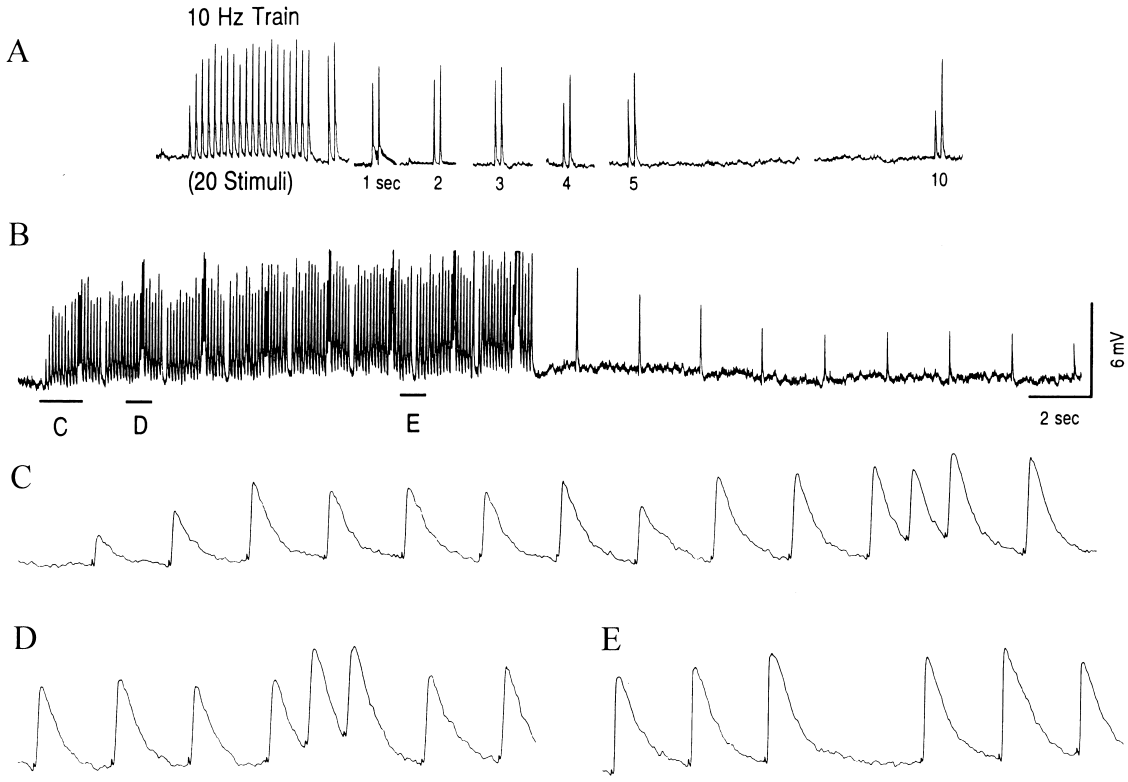

Fig. 7. Facilitation decays with a prolonged time-constant. (A) Following the induction of facilitation with the delivery of 20 stimuli at 10 Hz, a pair of identical stimuli were applied at varying intervals. Facilitation persists for approximately 10 s and therefore decays slowly. (B) Owing to the slow build-up and decay of facilitation, the addition or deletion of single stimuli do not have marked effects on this property (B–E). Corticothalamic EPSPs were isolated by including 50 mM QX-314 in the micropipette and with the local application of bicuculline methiodide (0.5–1 mM in micropipette).

increases in frequencies from 1–20 Hz (Fig. 6A). Increasing the frequency of stimulation to 50 Hz or higher gave rise to temporal summation of EPSPs as well as facilitation of EPSP amplitude (Fig. 6B, C).

The time-course of the persistence of facilitation was examined by applying a train of 20–200 stimuli followed at various intervals by a single test stimulus or a pair of stimuli ($n = 9$; Fig. 7). These experiments revealed that facilitation of monosynaptic corticothalamic inputs persists for approximately 10 s (Fig. 7A, B). The slow time-course of the build-up and decrement of facilitation is illustrated by the relative lack of effect of the insertion or deletion of single stimuli in a prolonged train (Fig. 7B–E).

Frequency dependence of GABAergic inhibitory postsynaptic potentials

Previously we have proposed that the strong activation of $GABA_B$ receptors in thalamocortical cells may require the prolonged and high-frequency discharge of GABAergic neurons in the thalamus.[3,25] Here we examined this hypothesis further through the repetitive stimulation in the region of the thalamic reticular nucleus following the block of EPSPs with bath application of CNQX (25 μM) and APV (50 μM). Under these circumstances, repetitive stimulation at 500 Hz resulted in a fast, presumed $GABA_A$ receptor mediated IPSP followed by a slow, presumed $GABA_B$ receptor-mediated IPSP (Fig. 8A). Applying either one, two, five, 10, 20, or 30 stimuli in the repetitive train resulted in varying degrees of activation of both fast and slow IPSPs in thalamocortical neurons (Fig. 8A, B). With only one electrical stimulus, a prominent fast IPSP is evoked and this is followed by a small slow IPSP (Fig. 8A, B). Increasing the number of stimuli to five results in a substantial enlargement in both the fast and slow IPSPs (Fig. 8A, B). However, increasing the number of stimuli further to 10, 20, or 30 results in a larger enhancement of the slow IPSP over that of the fast IPSP ($n = 4$, Fig. 8A, B).

In contrast to the potent effects of 500 Hz stimulation, repetitive stimulation at 50 Hz failed to yield strong activation of slow, presumed $GABA_B$ receptor-mediated IPSPs, even following the delivery of 30 stimuli (Fig. 8C, D). Similarly, the delivery of stimuli at 50 Hz also reduced the amplitude of the evoked fast IPSP in comparison with that obtained in the same neurons following stimulation at 500 Hz (Fig. 8).

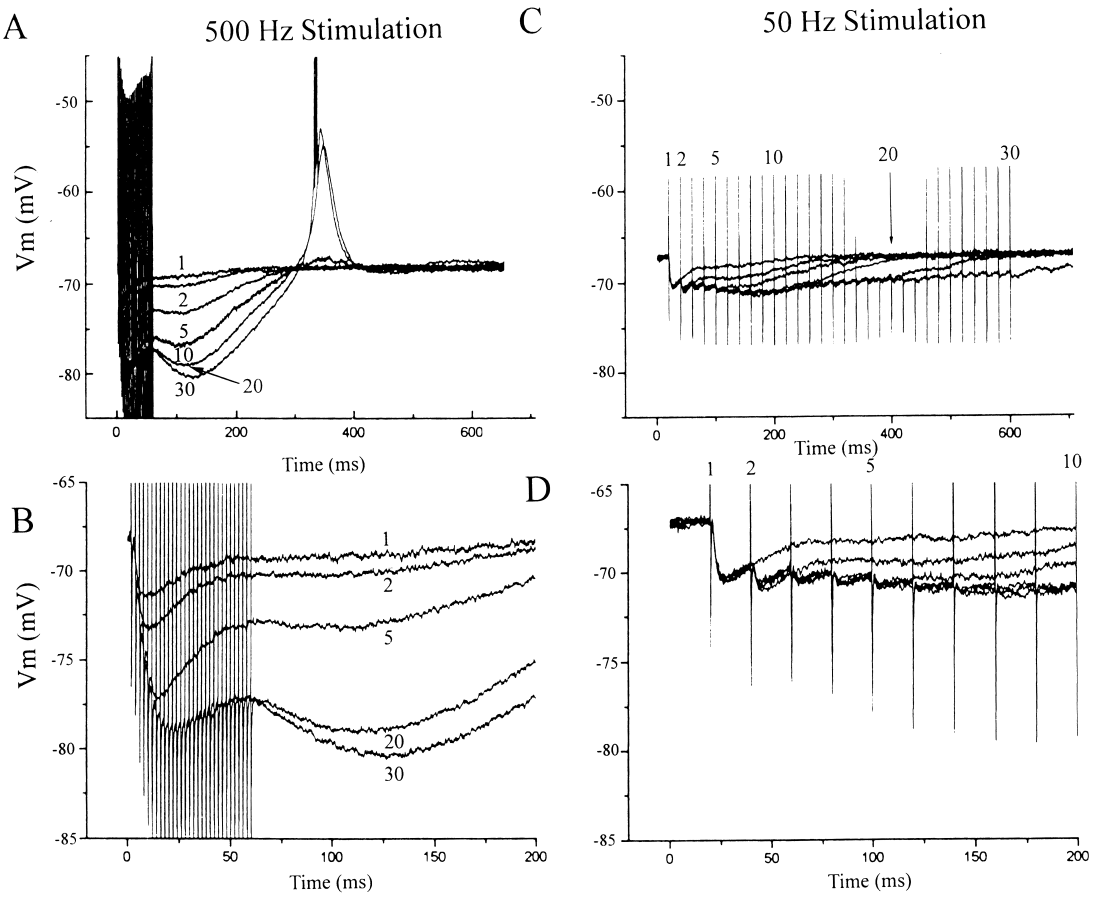

Fig. 8. Frequency of stimulation of NRT inputs to thalamocortical cells determines the degree to which $GABA_B$ receptors are activated. (A) Activation of fibers in the optic radiation at a frequency of 500 Hz results in robust fast and slow IPSPs in thalamocortical neurons (expanded in B for detail). Increasing the number of shocks delivered from one to two, five, 10, 20 and 30 results in a increase in the amplitude of both the early and late IPSPs. (C) In contrast, with stimulation at 50 Hz, increasing the number of stimuli does not markedly increase the peak amplitude of the early or late IPSP (expanded in D for detail).

Optic radiation stimulation evokes a slow excitatory postsynaptic potential through glutamate metabotropic receptors

Repetitive stimulation of the optic radiation could evoke a slow EPSP following the train of fast EPSPs and IPSPs ($n = 40$; Fig. 9A). This slow EPSP was elicited following the bath application of the muscarinic antagonist scopolamine (1 μM), the α_1-adrenoceptor antagonist prazosin (1 μM), the H_1 antagonist diphenhydramine (10 μM) and the serotoninergic antagonist methylsergide (1 μM). We have previously suggested that this slow EPSP may be mediated by the activation of glutamate metabotropic receptors, since it is occluded by maximal application of the exogenous agonist (1S,3R)-1-amino-1,3-cyclopentanedicarboxylic acid (1S,3R-ACPD).[34] Here we tested this hypothesis further through the local application of the glutamate metabotropic receptor antagonist α-methyl-4-carboxyphenylglycine (α-MCPG).[12] Local application of α-MCPG (5–10 mM in micropipette) resulted in a substantial reduction in the response of thalamocortical neurons to 1S,3R-ACPD ($55.2 \pm 14.8\%$ S.D.: $n = 8$: 5–10 μM in micropipette) as well as the amplitude of the slow corticothalamic EPSP (Fig. 9A, B; $57.1 \pm 14.0\%$ S.D.; $n = 33$). This effect of α-MCPG was reversible (Fig. 9). Close examination of the fast EPSPs and IPSPs evoked by corticothalamic stimulation reveals little change following the application of α-MCPG (see Fig. 9C).

DISCUSSION

The thalamus and cerebral cortex reciprocally innervate one another in a point-to-point manner that preserves, in the case of the lateral geniculate nucleus, retinotopic order.[34,56] In the cat, single fibers from the visual cortex densely innervate the A and C layers of the LGNd[37] and form synaptic terminals on both thalamocortical and local GABAergic interneurons.[23,36,45] These fibers also

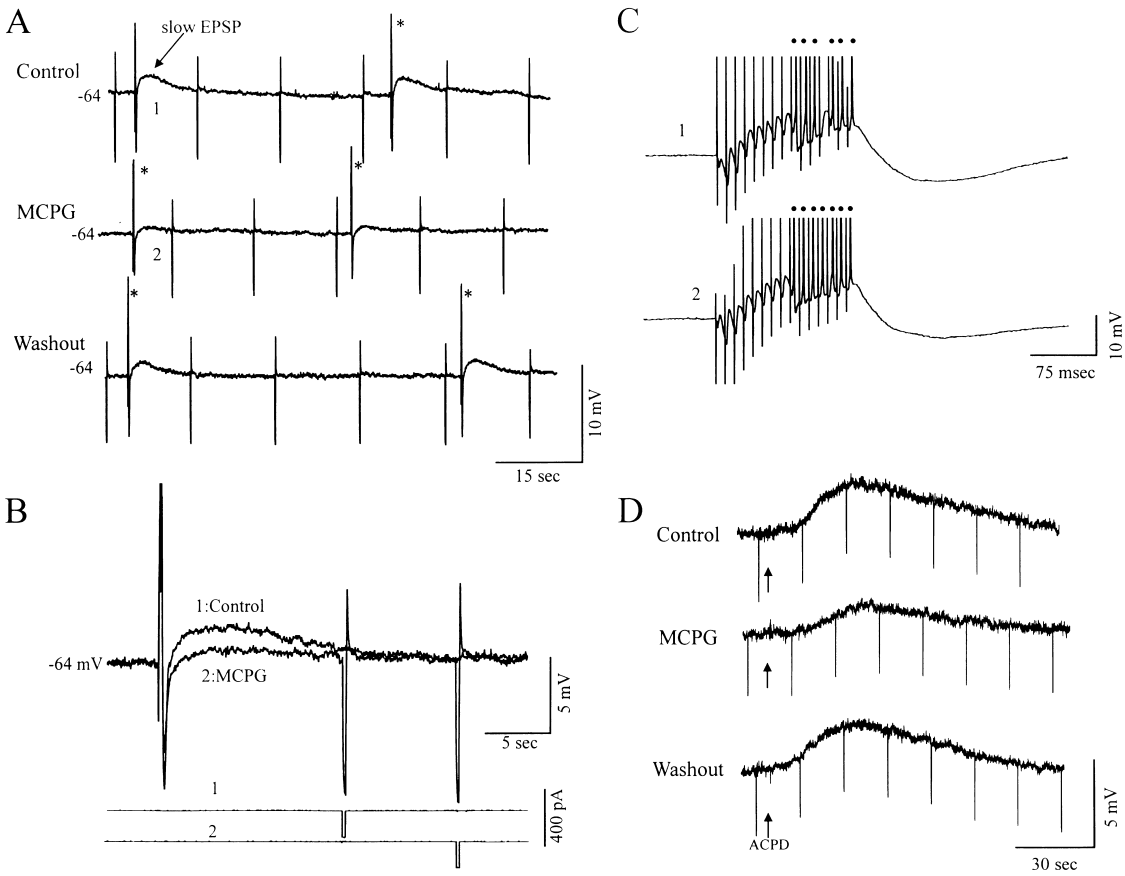

Fig. 9. Repetitive stimulation of the corticothalamic fibers results in a slow EPSP that is reduced by MCPG. (A) Repetitive electrical stimulation (15 stimuli at 100 Hz) results in a slow EPSP that lasts approximately 10 s. Local application of the glutamate metabotropic receptor antagonist MCPG results in a substantial reduction in the amplitude of the slow EPSP. This effect is reversible (washout). (B) Overlay of the slow EPSP before and after application of MCPG. (C) Expansion of the fast EPSPs and action potentials generated in response to the train of electrical stimuli before and after application of MCPG. (D) Local application of MCPG (10 mM in micropipette) results in a substantial reduction in the response of a thalamocortical cell to the local application of ACPD.

give rise to axon collaterals within the PGN and innervate these GABAergic neurons.[35,37]

Corticogeniculate neurons exert a monosynaptic excitatory influence on thalamocortical and perigeniculate/thalamic reticular neurons,[1,6,10,24,26] perhaps through the release of glutamate or aspartate (reviewed in Ref. 31). Repetitive activation of corticogeniculate inputs to thalamocortical cells, as well as to layer IV neurons in the primary visual cortex, results in frequency-dependent facilitation of the postsynaptic excitatory response[5,10,14,24,26,42,43,59] as well as prolonged (seconds) increases in excitability of thalamocortical cells.[10,34]

In the present study, we demonstrate that the repetitive stimulation of axons in the optic radiation results in EPSPs and IPSPs in thalamocortical neurons. The EPSPs presumably arise from activation of corticogeniculate axons, since axon collaterals between thalamocortical neurons are extremely rare.[16,37,47] The IPSPs examined in the present study may arise from either the activation of thalamic reticular neurons or their axons (either directly or indirectly) or through the activation of local GABAergic interneurons within the LGNd.[7,25] Pharmacologically, the corticogeniculate EPSPs are able to activate both non-NMDA and NMDA receptors,[11,24,48] while the evoked IPSPs are mediated through both $GABA_A$ and $GABA_B$ receptors. Repetitive stimulation of pharmacologically-isolated EPSPs resulted in marked facilitation at stimulation frequencies of 1 Hz or greater and this facilitation decayed with a time-constant of several seconds, a time-course that is most similar to synaptic augmentation.[15] Previously, it has been suggested that facilitation of the corticogeniculate pathway may result from the relief of voltage-dependent block of NMDA receptor activation.[10] However, our results indicate that this is not the mechanism of frequency-dependent facilitation of corticogeniculate synapses. This facilitation was present even following the pharmacological block of NMDA receptors or the removal of Mg^{2+} from the bathing medium (see Fig. 5). Instead, our results are most consistent with an increase in release of

neurotransmitter from corticogeniculate terminals during facilitation, as has been demonstrated in other neuronal systems (reviewed in Refs 15 and 28). Detailed investigations of the cellular mechanisms of synaptic facilitation have repeatedly demonstrated a crucial role of the dynamics of Ca^{2+} mediated processes in presynaptic terminals (reviewed in Refs 10 and 62).

In addition to facilitation of corticogeniculate synaptic transmission, repetitive stimulation of isolated IPSPs, presumably representing the activation of thalamic reticular axons, resulted in synaptic depression. Similarly, dual intracellular recordings from monosynaptically-coupled pairs of PGN and LGNd neurons have demonstrated that repetitive discharge of PGN neurons results in depression of the postsynaptic IPSP.[25a] In the hippocampus, depression of GABAergic IPSPs following repetitive stimulation results largely through the presynaptic inhibition of GABA release owing to the activation of $GABA_B$ receptor (reviewed in Ref. 54), which appears to operate mainly through a decrease in Ca^{2+} conductances.[27,61] Similarly in thalamocortical neurons, activation of presynaptic $GABA_B$ receptors results in a substantial decrease in the release of GABA from NRT terminals[47,57] and block of $GABA_B$ receptors results in a reduction in paired pulse depression of GABA release.[57] Another possible mechanism for the depression of IPSPs observed here is the accumulation of Cl^- in the postsynaptic cell,[55] although the contribution of this mechanism to depression of IPSPs in thalamocortical neurons remains to be examined.

Together, the process of synaptic facilitation of corticogeniculate synapses and depression of GABAergic pathways imparts on the corticogeniculate pathway the ability to exhibit predominately inhibitory or excitatory effects, depending upon the frequency of stimulation. At low frequencies (e.g., < 1 Hz) activation of the corticogeniculate pathway may result in prominent IPSPs in thalamocortical neurons owing to excitation of thalamic reticular and intra-nuclear GABAergic neurons. However, at higher frequencies of activation, this inhibitory response gives way to pronounced and direct EPSPs. An additional factor to consider is the ongoing activity of thalamic reticular and intrathalamic interneurons, even in the absence of corticogeniculate activation. The spontaneous or evoked activity of these cell types will likely result in a baseline level of presynaptic inhibition of GABA release. Activation of corticothalamic axons in this case may, therefore, result in prominent excitatory effects from the very beginning of repetitive stimulation.

Corticogeniculate fibers activate a slow excitatory postsynaptic potential

We have previously demonstrated that the repetitive stimulation of corticogeniculate fibers in the guinea-pig LGNd results not only in the generation of fast, monosynaptic EPSPs, but also in the generation of a slow EPSP that has a latency to peak of several seconds and that may persist for up to 1 min.[37] This slow EPSP persists following the block of muscarinic, α and β adrenergic, serotoninergic, and H_1 and H_2 histaminergic receptors and is occluded by the maximal stimulation of glutamate metabotropic receptors. Here we demonstrate that the antagonism of glutamate metabotropic receptors results in a substantial reduction of the corticogeniculate slow EPSP, confirming that this event is mediated through the activation of these receptors.

Eight different subtypes of metabotropic glutamate receptor have been cloned and have been segregated into three different groups based upon the postsynaptic responses they induce, their sequence similarities, and pharmacology (for review see Refs 38 and 44). In the thalamus, metabotropic glutamate receptor 1 has been demonstrated by both *in situ* hybridization[30,50] as well as immunocytochemistry.[4,19,29,58] Examination at the electron microscopic level has revealed that metabotropic receptor 1a, a splice variant of metabotropic glutamate receptor 1, is prominent in the distal, corticorecipient, zones of thalamocortical neurons[58] and pharmacological analysis of corticothalamic slow EPSPs suggest that they are mediated by group I metabotropic receptors.[11] These results suggest that the corticothalamic synapses operate through the activation of both ionotropic AMPA/kainate and NMDA receptors and glutamate metabotropic receptors. Electron microscopic results have suggested that glutamate metabotropic receptors may be localized adjacent to synaptic terminals, and are therefore activated by "spill over" of glutamate,[4,19,58] thereby presumably requiring a more intense release of glutamate for their activation. This possibility remains to be carefully examined in the corticogeniculate pathway.

Recent results suggest that there may exist an important glutamatergic input to thalamocortical neurons from the brainstem.[13] Whether or not these glutamatergic synapses may also activate metabotropic receptors, and therefore contribute to the ascending control of thalamocortical activity through modulation of the membrane potential of these cells, is unknown. Since these brainstem inputs also synapse onto the dendrites of thalamocortical cell and appear morphologically similar to corticogeniculate synapses it is likely that metabotropic glutamate 1a receptors are also adjacent to these brainstem inputs.

Functional properties of corticogeniculate transmission

Despite numerous *in vivo* investigations, the

functional role of the massive corticothalamic projection is still not well understood. In general, inactivation of the cerebral cortex results in a decrease in excitability of thalamocortical neurons, a result which is consistent with the direct excitatory effects of this pathway[17,18] (reviewed in Ref. 53). However, other studies have also found increases in responsiveness of some thalamic neurons following inactivation of the cerebral cortex, suggesting that the functional role of this pathway may be complex. One important feature in determining the excitatory or inhibitory influence of the corticogeniculate path is the spatial distribution of afferent fibers between these two structures.[56] Here we also demonstrate that the temporal structure of activation of corticothalamic pathway is important in determining the functional influence of layer VI on thalamocortical responsiveness. At low frequencies of activation, the inhibitory influence of activation of thalamic reticular or local interneurons are likely to dominate. However, upon higher frequency stimulation, or repetitive stimulation, these inhibitory influences should undergo frequency-dependent depression. At the same time, the monosynaptic corticothalamic EPSPs would undergo synaptic facilitation, resulting in a switch from predominately inhibitory to excitatory interactions between the cortex and thalamus (see Figs 2 and 3). Repeated activation of corticothalamic inputs may also result in a slow depolarization of thalamocortical cells through the activation of glutamate metabotropic receptors. This slow depolarization will result in an enhancement of the tonic, single spike mode of action potential generation in thalamocortical cells and a suppression of intrinsic and network-based low-frequency oscillations.

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REFERENCES

1. Ahlsen G., Grant K. and Lindstrom S. (1982) Monosynaptic excitation of principal cells in the lateral geniculate nucleus by corticofugal fibers. *Brain Res.* **234**, 454–458.
2. Andersen P., Junge K. and Sveen O. (1967) Cortico-thalamic facilitation of somatosensory impulses. *Nature* **214**, 1011–1012.
3. Bal T., von Krosigk M. and McCormick D. A. (1995) Synaptic and membrane mechanisms underlying synchronized oscillations in the ferret lateral geniculate nucleus *in vitro*. *J. Physiol., Lond.* **483**, 641–663.
4. Baude A., Nusser Z., Roberts J. D. B., Mulvihill E., McIlhinney R. A. J. and Somogyi P. (1993) The metabotropic glutamate receptor (mGluR1a) is concentrated at perisynaptic membrane of neuronal subpopulations as detected by immunogold reaction. *Neuron* **11**, 771–787.
5. Castro-Alamancos M. A., Landisman C. E. and Connors B. W. (1997) Mechanisms of facilitation at corticothalamic synapses in the ventrobasal thalamus. *Soc. Neurosci. Abstr.* **23**, 574.
6. Contreras D. and Steriade M. (1996) Spindle oscillation in cats: the role of corticothalamic feedback in a thalamically generated rhythm. *J. Physiol.* **490**, 159–179.
7. Crunelli V., Haby M., Jassik-Gerschenfeld D., Leresche N. and Pirchio M. (1988) Cl^-- and K^+-dependent inhibitory postsynaptic potentials evoked by interneurones of the rat lateral geniculate nucleus. *J. Physiol., Lond.* **399**, 153–176.
8. Davies C. H., Davies S. N. and Collingridge G. L. (1990) Paired-pulse depression of monosynaptic GABA-mediated inhibitory postsynaptic responses in rat hippocampus. *J. Physiol., Lond.* **424**, 513–531.
9. Deisz R. A. and Prince D. A. (1989) Frequency-dependent depression of inhibition in guinea-pig neocortex *in vitro* by GABAB receptor feed-back on GABA release. *J. Physiol., Lond.* **412**, 513–541.
10. Deschênes M. and Hu B. (1990) Electrophysiology and pharmacology of the corticothalamic input to lateral thalamic nuclei: an intracellular study in the cat. *Eur. J. Neurosci.* **2**, 140–152.
11. Eaton S. A. and Salt T. E. (1996) Role of *N*-methyl-D-aspartate and metabotropic glutamate receptors in corticothalamic excitatory postsynaptic potentials *in vivo*. *Neuroscience* **73**, 1–5.
12. Eaton S. A., Jane D. E., Jones P. L. St. J., Porter R. H. P., Pook P. C.-K., Sunter D. C., Udvarhelyi P. M., Roberts P. J., Salt T. E. and Watkins J. C. (1993) Competitive antagonism at metabotropic glutamate receptors by (S)-4-carboxyphenlglycine (CGP) and (RS)-α-methyl-carboxyphenylglycine (MCPG). *Eur. J. Pharmac.* **244**, 195–197.
13. Erisir A., van Horn S. C., Bickford M. E. and Sherman S. M. (1997) Immunocytochemistry and distribution of parabrachial terminals in the lateral geniculate nucleus of the cat: a comparison with corticogeniculate terminals. *J. comp. Neurol.* **377**, 535–549.
14. Ferster D. and Lindstrom S. (1985) Augmenting responses evoked in area 17 of the cat by intracortical axon collaterals of cortico-geniculate cells. *J. Physiol., Lond.* **367**, 217–232.
15. Fisher S. A., Fisher T. M. and Carew T. J. (1997) Multiple overlapping processes underlying short-term synaptic enhancement. *Trends Neurosci.* **20**, 170–177.
16. Friedlander M. J., Lin C. S., Stanford L. R. and Sherman S. M. (1981) Morphology of functionally identified neurones in the lateral geniculate nucleus of the cat. *J. Neurophysiol.* **46**, 80–129.
17. Funke K. and Eysel U. T. (1992) EEG-dependent modulation of response dynamics of cat dLGN relay cells and the contribution of corticogeniculate feedback. *Brain Res.* **573**, 217–227.
18. Ghosh S., Murray G. M., Turman A. B. and Rowe M. J. (1994) Corticothalamic influences on transmission of tactile information in the ventroposterolateral thalamus of the cat: effect of reversible inactivation of somatosensory cortical areas I and II. *Expl Brain Res.* **100**, 276–286.
19. Godwin D. W., van Horn S. C., Erisir A., Sesma M., Romano C. and Sherman S. M. (1996) Ultrastructural localization suggests that retinal and cortical inputs access different metabotropic glutamate receptors in the lateral geniculate nucleus. *J. Neurosci.* **16**, 8181–8192.
20. Hirsch J. C., Fourment A. and Marc M. E. (1983) Sleep-related variations of membrane potential in the lateral geniculate body relay neurons of the cat. *Brain Res.* **259**, 308–312.

21. Izzo P. N. (1991) A note on the use of biocytin in anterograde tracing studies in the central nervous system: application at both light and electron microscopic level. *J. Neurosci. Meth.* **273**, 155–166.
22. Jones E. G. (1985) *The Thalamus*. Plenum, New York.
23. Jones E. G. and Powell T. P. S. (1969) An electron microscopic study of the mode of termination of cortico-thalamic fibres within the sensory relay nuclei of the thalamus. *Proc. R. Soc. Lond.* **172**, 173–185.
24. Kao C. and Coulter D. A. (1997) Physiology and pharmacology of corticothalamic stimulation-evoked responses in rat somatosensory thalamic neurons *in vitro*. *J. Neurophysiol.* **77**, 2661–2676.
25. Kim U., Sanchez-Vives M. V. and McCormick D. A. (1997) Functional dynamics of GABAergic inhibition in the thalamus. *Science* **278**, 130–134.
25a. Kim U. and McCormick D. A. (1998) The functional influence of burst and tonic firing mode on synaptic interactions in the thalamus. *J. Neurosci.* **18**, 9500–9516.
26. Lindström S. and Wrobel A. (1990) Frequency dependent corticofugal excitation of principal cells in the cat's dorsal lateral geniculate nucleus. *Expl Brain Res.* **79**, 313–318.
27. Lüscher C., Jan L. Y., Stoffel M., Malenka R. C. and Nicoll R. A. (1997) G protein-coupled inwardly rectifying K^+ channels (GIRKs) mediate postsynaptic but not presynaptic transmitter actions in hippocampal neurons. *Neuron* **19**, 687–695.
28. Magleby K. L. (1987) Short-term changes in synaptic efficacy. In *Synaptic Function* (eds Edelman G. M., Gall W. E. and Cowan W. M.), John Wiley and Sons, New York.
29. Martin L. J., Blackstone C. D., Huganir R. L. and Price D. L. (1992) Cellular localization of a metabotropic glutamate receptor in rat brain. *Neuron* **9**, 259–270.
30. Masu M., Tanabe Y., Tsuchida K., Shigemoto R. and Nakanishi S. (1991) Sequence and expression of a metabotropic glutamate receptor. *Nature* **349**, 760–765.
31. McCormick D. A. (1992) Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. *Prog. Neurobiol.* **39**, 337–388.
32. McCormick D. A. and Prince D. A. (1987) Actions of acetylcholine in the guinea-pig and cat medial and lateral geniculate nuclei, *in vitro*. *J. Physiol., Lond.* **392**, 147–165.
33. McCormick D. A. and Prince D. A. (1988) Noradrenergic modulation of firing pattern in guinea pig and cat thalamic neurons, *in vitro*. *J. Neurophysiol.* **59**, 978–996.
34. McCormick D. A. and von Krosigk M. (1992) Corticothalamic activation modulates thalamic firing through glutamate metabotropic receptors. *Proc. natn. Acad. Sci. U.S.A.* **89**, 2774–2778.
35. Montero V. M. (1989) Ultrastructural identification of synaptic terminals from cortical axons and from collateral axons of geniculo-cortical relay cells in the perigeniculate nucleus of the cat. *Expl Brain Res.* **75**, 65–72.
36. Montero V. M. (1991) A quantitative study of synaptic contacts on interneurons and relay cells of the cat lateral geniculate nucleus. *Expl Brain Res.* **86**, 257–270.
37. Murphy P. C. and Sillito A. M. (1996) Functional morphology of the feedback pathway from area 17 of the cat visual cortex to the lateral geniculate nucleus. *J. Neurosci.* **16**, 1180–1192.
38. Nakanishi S. (1992) Molecular diversity of glutamate receptors and implications for brain function. *Science* **258**, 597–603.
39. Nathan T., Jensen M. S. and Lambert J. D. (1990) The slow inhibitory postsynaptic potential in rat hippocampal CA1 neurones is blocked by intracellular injection of QX-314. *Neurosci. Lett.* **110**, 309–313.
40. Nathan T. and Lambert J. D. (1991) Depression of the fast IPSP underlies paired-pulse facilitation in area CA1 of the rat hippocampus. *J. Neurophysiol.* **66**, 1704–1715.
41. Paulsen O. and Heggelund P. (1994) The quantal size at retinogeniculate synapses determined from spontaneous and evoked EPSCs in guinea-pig thalamic slices. *J. Physiol.* **480**, 505–511.
42. Paulsen O., Kielland A. and Heggelund P. (1997) Two major excitatory inputs on dLGN neurones show distinct synaptic properties. *Soc. Neurosci. Abstr.* **23**, 1540.
43. Pedoarena C. and Llinás R. (1997) Gamma band activation of the corticothalamic (CT) pathway results in a distinct short term facilitation: an *in vitro* study. *Soc. Neurosci. Abstr.* **23**, 1010.
44. Pin J.-P. and Duvoisin R. (1995) Review: neurotransmitter receptors. I. The metabotropic glutamate receptors: structure and functions. *Neuropharmacology* **34**, 1–26.
45. Robson J. A. (1983) The morphology of corticofugal axons to the dorsal lateral geniculate nucleus in the cat. *J. comp. Neurol.* **216**, 89–103.
46. Robson J. A. (1984) Reconstructions of corticogeniculate axons in the cat. *J. comp. Neurol.* **225**, 193–200.
47. Sanchez-Vives M. V. and McCormick D. A. (1997) Functional properties of perigeniculate inhibition of dorsal lateral geniculate nucleus thalamocortical neurons *in vitro*. *J. Neurosci.* **17**, 8880–8893.
48. Scharfman H. E., Lu S. M., Guido W., Adams P. R. and Sherman S. M. (1990) *N*-methyl-D-aspartate receptors contribute to excitatory postsynaptic potentials of cat lateral geniculate neurons recorded in thalamic slices. *Proc. natn. Acad. Sci. U.S.A.* **87**, 4548–4552.
49. Sherman S. M. and Guillery R. W. (1996) Functional organization of thalamocortical relays. *J. Neurophysiol.* **76**, 1367–1395.
50. Shigemoto R., Nakanishi S. and Mizuno N. (1992) Distribution of the nRNA for a metabotropic glutamate receptor (mGluR1) in the central nervous system: an *in situ* hybridization study in adult and developing rat. *J. comp. Neurol.* **322**, 121–135.
51. Steriade M., McCormick D. A. and Sejnowski T. J. (1993) Thalamocortical oscillations in the sleeping and aroused brain. *Science* **262**, 679–685.
52. Steriade M. and McCarley R. W. (1989) *Brainstem Control of Wakefulness and Sleep*. Plenum, New York.
53. Steriade M., Jones, E. G. and McCormick D. A. (1997) *Thalamus*. Vol. 1. *Organization and Function*. Elsevier Science, New York.
54. Thompson S. M., Capogna M. and Scanziani M. (1993) Presynaptic inhibition in the hippocampus. *Trends Neurosci.* **16**, 222–227.
55. Thompson S. M. and Gahwiler B. H. (1989) Activity-dependent disinhibition. I. Repetitive stimulation reduces IPSP driving force and conductance in the hippocampus *in vitro*. *J. Neurophysiol.* **61**, 501–511.
56. Tsumoto T., Creutzfeldt O. D. and Legendy C. R. (1978) Functional organization of the corticofugal system from visual cortex to lateral geniculate nucleus in the cat (with an appendix on geniculo-cortical monosynaptic connections). *Expl Brain Res.* **32**, 345–364.

57. Ulrich D. and Huguenard J. R. (1996) $GABA_B$ receptor-mediated responses in GABAergic projection neurones of rat nucleus reticularis thalami *in vitro*. *J. Physiol.* **493**, 845–854.
58. Vidnyánszky Z., Görcs T. J., Négyessy L., Borostyánköi Z., Kuhn R., Knöpfel T. and Hámori J. (1996) Immunocytochemical visualization of the mGluR1a metabotropic glutamate receptor at synapses of corticothalamic terminals originating from Area 17 of the rat. *Eur. J. Neurosci.* **8**, 1061–1071.
59. von Krosigk M. and McCormick D. A. (1992) Mechanisms of frequency dependent facilitation of corticothalamic EPSPs. *Soc. Neurosci. Abstr.* **18**, 140.
60. Woodward W. R., Chiaia N., Teyler T. J., Leong L. and Coull B. M. (1990) Organization of cortical afferent and efferent pathways in the white matter of the rat visual system. *Neuroscience* **36**, 393–401.
61. Wu L. G. and Saggau P. (1995) $GABA_B$ receptor-mediated presynaptic inhibition in guinea-pig hippocampus is caused by reduction of presynaptic Ca^{2+} influx. *J. Physiol.* **485**, 649–657.
62. Zucker R. S. (1989) Short-term synaptic plasticity. *A. Rev. Neurosci.* **12**, 13–31.

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