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Pattern and Pharmacology of Propagating Epileptiform Activity in Mouse Cerebral Cortex

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Multiple extracellular recording electrodes were used to study the intra- and interhemispheric spread of stimulus-evoked epileptiform responses in adult mouse neocortical slices. Bath application of 20 μM bicuculline methiodide induced epileptiform activity that propagated at ~0.08 m/s over several millimeters in rostro-caudal and medio-lateral direction within the ipsilateral hemisphere and across the corpus callosum to the contralateral hemisphere. A vertical incision from layer II to subcortical regions did not prevent the spread to remote cortical regions, indicating that layer I plays a major role in the lateral propagation of epileptiform activity. The intra- and interhemispheric spread was not influenced by application of an *N*-methyl-D-aspartate (NMDA) receptor antagonist, but blocked by an antagonist acting at the (±)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-type glutamate receptor. The potential role of potassium channel activation in controlling the generation or spread of epileptiform activity was tested by applying the potassium channel opener cromakalim and the serotonin type 1A (5-HT_{1A}) receptor agonist (±)-8-hydroxydipropylaminotetralin (8-OH-DPAT) to the disinhibited slices. Whereas cromakalim reduced the neuronal excitability and blocked all epileptiform responses, 8-OH-DAPT did not affect the activity pattern. Our results suggest that propagating epileptiform activity in disinhibited neocortical structures is predominantly mediated by activation of AMPA receptors and controllable by activation of a voltage-dependent potassium current. © 1998 Academic Press

Key Words: **epilepsy; propagation; bicuculline; AMPA receptor; NMDA receptor; 5-HT_{1A} receptor; cromakalim; extracellular recordings; neocortical slice; mouse**

INTRODUCTION

Despite the enormous progress in the development of new antiepileptic drugs, 10–20% of all epileptic seizures are still refractory to current drug therapy (18, 27). To understand the cellular and molecular mechanisms underlying the generation and also the propagation of epileptic seizures, different experimental approaches are available. Whereas the mechanisms leading to the generation of epileptiform discharges can be studied by the use of intracellular recording techniques, the widespread propagation of this pathophysiological activity can be best analyzed with imaging techniques (1, 13, 35) or multiple, usually extracellular, recording electrodes (8, 23). The *in vitro* brain slice preparation offers the advantage of studying both processes under good experimental control, since the role of different receptors and the effects of potential anticonvulsants can be easily investigated by applying these compounds to the extracellular bathing medium. In order to examine the intracortical and commissural spread of epileptiform activity and its modification by ionotropic glutamate receptor antagonists or potassium channel agonists, we used the *in vitro* slice preparation of the adult mouse cerebral cortex. Due to its small size the mouse brain has the advantage that a large body of the synaptic circuitry can be preserved in a 400-μm slice. Furthermore, sagittal slices including the whole cortical hemisphere or whole brain coronal slices with intact corpus callosum can be easily prepared to study the widespread intra- and interhemispheric propagation of epileptiform activity.

Epileptiform activity *in vivo* and *in vitro* can be induced by partial or complete blockade of synaptic inhibition mediated by γ-amino butyric acid (GABA) (14). Especially antagonists acting at the $GABA_A$ receptor subtype, like bicuculline, are most effective in generating epileptiform responses (12, 16, 21). The bicuculline model is very useful for studying the propagation pattern of epileptiform activity and its underlying pharmacology, since high bicuculline concentra-

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tions of ≥10 μM induce a stereotyped and reliable intracortical spread of epileptiform responses (1, 8, 11). Using this model, intracellular recordings have been used to study the participation of the different ionotropic glutamate receptors in the generation of the stimulus-induced paroxysmal depolarization shift (PDS) (20, 24). In contrast, the role of these receptors in the spread of epileptiform activity in the mature neocortex has not been studied. In the present study, the "high bicuculline model" was used to examine the widespread intracortical and commissural propagation pattern of stimulus-evoked epileptiform activity and its sensitivity to ionotropic glutamate receptor antagonists. Furthermore we studied the influence of a 5-HT_{1A} receptor agonist in this model since a recent study suggests that serotonin may be a promising anticonvulsant in the entorhinal cortex (33). An anticonvulsant action has been also demonstrated in the hippocampus for the unspecific potassium channel opener cromakalim (BRL 34915) (2, 3), but so far not in the cerebral cortex. We therefore tested this compound in the high bicuculline model of the mouse neocortical slice preparation.

METHODS

Slice Preparation

Sixty-eight adult (45–70 days) NMRI mice were deeply anaesthetized by an intraperitoneal injection of pentobarbital sodium (50 mg/kg body weight) and decapitated. The brain was rapidly removed and stored for 1–2 min in ice-cold artificial cerebrospinal fluid (ACSF) consisting of (in mM) 124 NaCl, 3 KCl, 1.25 NaH_2PO_4, 1.8 $MgCl_2$, 1.6 $CaCl_2$, 26 $NaHCO_3$, and 10 glucose with a pH of 7.4 when saturated with 95% O_2–5% CO_2. Whole brain coronal or sagittal slices with a nominal thickness of 400 μm were cut on a Dosaka vibratome (Kyoto/Japan). Coronal slices with intact corpus callosum or whole brain sagittal slices were transferred to an incubation-storage chamber or to an interface-time recording chamber and kept at 32–33°C and 34–35°C, respectively. Slices were allowed to recover for at least 1 h before recording began.

Recording Techniques

Extracellular recordings were performed with two arrays of four tungsten 4- to 5-MΩ microelectrodes (FHC, Brunswick, USA), which were separated by approximately 0.5 mm. In coronal and sagittal slices, these electrodes were positioned in layers II/III in medio-lateral and rostro-caudal directions, respectively. This configuration allowed the recording of extracellular signals over a distance of ≥3.5 mm with a spatial resolution of 0.5 mm without repositioning of the recording electrodes. In coronal slices, the recording electrodes were located in the parietal ("barrel") cortex (34). In sagittal slices, field potential responses over a horizontal distance of 5.5 mm were recorded in the frontal cortex, hindlimb area, and occipital cortex by repositioning of the first electrode array to a more distant recording site. This manipulation did not affect the responsiveness of the slice, since the signals recorded with the fixed second electrode array were unchanged. The stimulating electrode consisted of two sharpened tungsten wires with a tip distance of 150–200 μm. This electrode was located in layer VI below the first recording electrode. Orthodromic synaptic responses were evoked by electrical stimulation with 200-μs pulses at intervals of 10–30 s. Signals were AC recorded with eight separate extracellular amplifiers, lowpass filtered at 3 kHz, stored, and analyzed with an eight-channel PC-based software program (TIDA, Heka elektronik, Lambrecht, Germany).

Pharmacology

Epileptiform activity was induced by bath application of the $GABA_A$ antagonist bicuculline methiodide (BMI, Sigma) in a concentration of 20 μM. For pharmacological analyses, the NMDA antagonist DL-2-amino-5-phosphonovaleric acid (APV, Sigma; 30 μM), the AMPA antagonist 6-nitro-7-sulphamoylbenzo[*f*]quinoxaline-2,3-dione (NBQX, Novo Nordisk, 10 μM), the potassium channel opener cromakalim [(±)6-cyano-3,4-dihydro-2,2-dimethyl-*trans*-4-(2-oxo-1-pyrrolidyl)-2H -benzo[*b*-]pyran-3-ol, Sigma; 300 μM], and the 5-HT_{1A} agonist (±)-8-hydroxy-dipropylaminotetralin (8-OH-DPAT, RBI, 30 μM) were bath applied and washed in for at least 30 min before subsequent recording.

Data Analysis and Statistics

Stimulus-evoked field potential responses were analyzed in their amplitude from the minimum of the negative going component to the peak of the next positive going component. All field potential responses were normalized to the response amplitude measured at the first recording electrode in normal bathing solution. The spread of BMI-induced epileptiform activity was analyzed in its average velocity by plotting for each recording site the latency from stimulus to the field potential peak amplitude versus the distance from the first recording electrode. The reciprocal of the slope as estimated from the linear regression analysis of this plot gave the average velocity of spread. For this analysis, the exact tip separation between the recording electrodes was determined by photographing the electrode array under a microscope and measuring the distance between two neighboring electrodes. The Student *t* test was used for statistical analyses. If not otherwise noted, values throughout this report are expressed as mean ± standard error of the mean (SEM).

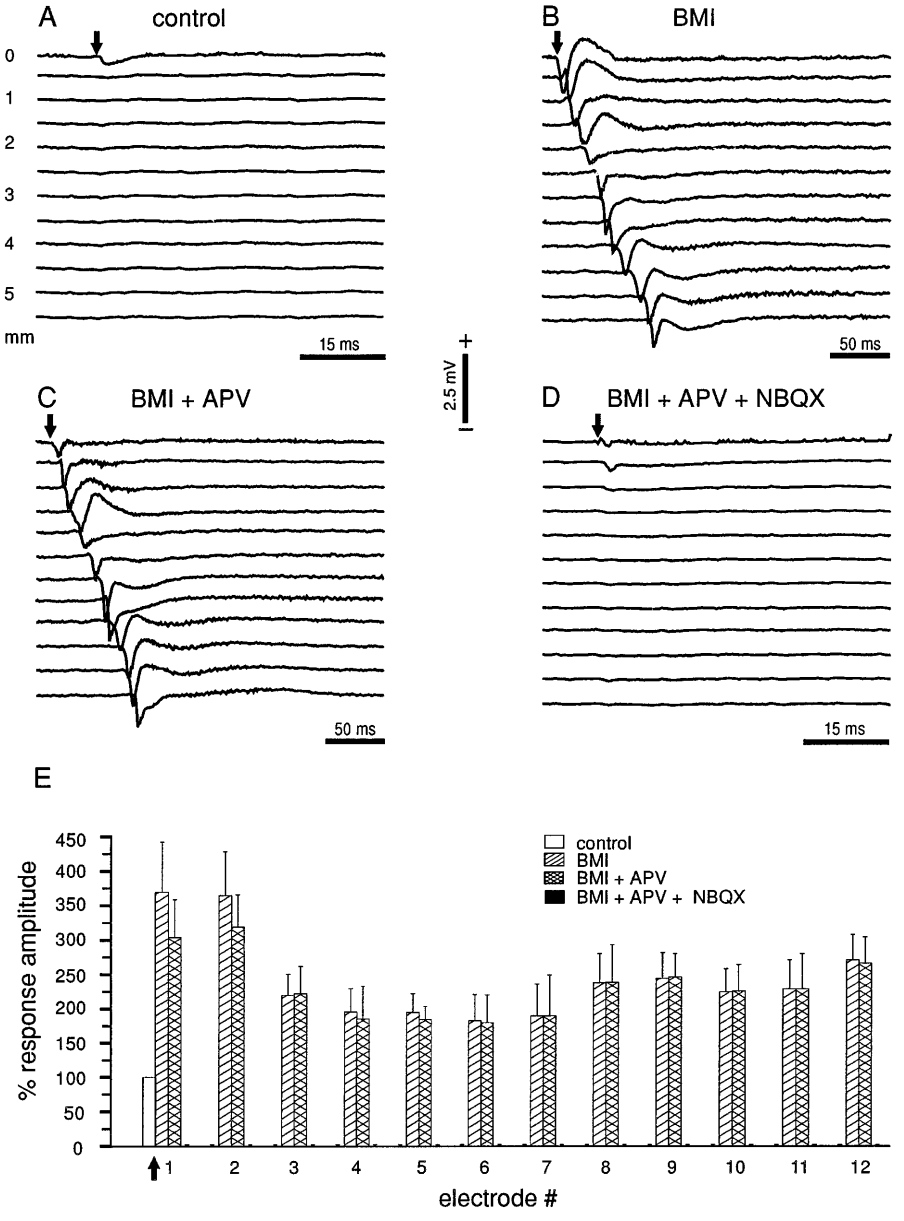

FIG. 1. (A–D) Spread of stimulus-evoked field potential responses in a sagittal neocortical slice from an adult mouse under control conditions (A), after washin of 20 μM bicuculline methiodide (BMI) (B), and after addition of 30 μM APV (C) and 10 μM NBQX (D). Field potentials were recorded at 12 different supragranular sites separated by approximately 0.5 mm. The stimulating electrode was located below the first recording electrode at position 0 mm (↓ in A–D). Note spatial restriction of field potential response to first electrode under control conditions and continuous propagation of larger response in BMI. The spread of epileptiform activity is not influenced by APV, but blocked by NBQX. (E) Quantitative results on the influence of $GABA_A$ receptor blockade and application of ionotropic glutamate receptors antagonists on the rostro-caudal propagation of stimulus-evoked field potential responses in mouse sagittal slices ($n = 9$). In this and the following figures, all data are expressed as mean ± SEM.

RESULTS

Intracortical Horizontal Propagation of Epileptiform Activity

The intracortical horizontal spread of stimulus-evoked activity was studied in sagittal and coronal slices from the adult mouse. Under control conditions in normal bathing solution, low intensity (2–4 V) orthodromic synaptic stimuli in layer VI elicited a response, which was restricted to the activated column of ≤1 mm in diameter. In sagittal slices, the response at the first recording electrode amounted to 0.44 ± 0.06 mV ($n = 9$). No response could be observed at the other 11 recording sites under this condition (Fig. 1A and open bars in Fig. 1E). In coronal slices, a synaptic response could be observed 0.5 mm lateral from the

stimulating site, but at this location the amplitude amounted only to 20.4 ± 8.5% (n = 8) of the average field potential amplitude recorded above the stimulating electrode (not shown). A pronounced increase in the activity spread could be observed after blockade of the $GABA_A$ receptor with 20 μM BMI (Fig. 1B). In sagittal slices, the response amplitude at the first recording site increased on average to 364 ± 64% and reached an average amplitude >180% at all other recording sites (hatched bars in Fig. 1E). Even at the most distant recording site located 5.5 mm caudal from the site of stimulation, the absolute response amplitude amounted to 1.15 ± 0.15 mV (n = 9), indicating an activation of remote regions. Bath application of 30 μM APV did not significantly alter this propagation pattern (Fig. 1C). The relative response amplitude at all recording sites was still >180% (cross-hatched bars in Fig. 1E), suggesting that NMDA receptors play a minor role in the lateral intracortical spread of epileptiform activity. However, addition of 10 μM NBQX to the APV-containing bathing solution blocked all orthodromic responses and also the propagation of epileptiform responses, indicating that AMPA receptors are required for the horizontal spread (Figs. 1D, 1E). An identical pharmacological profile could be obtained in coronal slices for the propagation of stimulus-evoked epileptiform responses in the medio-lateral direction (not shown). Bath application of 20 μM BMI caused a 230.6 ± 22.6% (n = 8) increase in the response amplitude at the first recording electrode and a lateral spread of activity over a distance of ≥3.5 mm. Whereas 30 μM APV did not influence this pattern, addition of 10 μM NBQX blocked all orthodromic synaptic responses and the spread of epileptiform activity.

The average intracortical propagation velocity in disinhibited neocortical slices was calculated by linear regression from a plot of the response latency versus the lateral distance of the recording site from the stimulating electrode (Fig. 2). The stimulus-evoked epileptiform response propagated uniformly in rostro-caudal direction with an average velocity of 77.4 mm/s to the most distant recording site (R^2 = 0.95, n = 108; ○ in Fig. 2). Addition of APV did not alter the velocity (77.6 mm/s, R^2 = 0.92, n = 108; ● in Fig. 2). A very similar velocity could be determined in coronal slices for the medio-lateral spread (90 mm/s).

The intrinsic circuitry underlying the spread of epileptiform responses was studied in coronal slices by performing a vertical incision through the cortex and all subcortical regions leaving only layer I intact (Fig. 3). This cut of all horizontal fiber tracts located in layers II–VI, the white matter, and subcortical areas did not block the widespread propagation of epileptiform responses. Sagittal slices (n = 9), which were disinhibited by 20 μM BMI, revealed the usual pattern of rostro-caudal spread (Fig. 4A; open bars in Fig. 4C). After performing a vertical incision as illustrated in Fig. 3, electrical stimulation below the first recording electrode elicited a propagating epileptiform response. Although the velocity of spread was unchanged, the amplitudes of the responses recorded at electrodes 5–8 were significantly ($P < 0.05$) reduced after the cut by

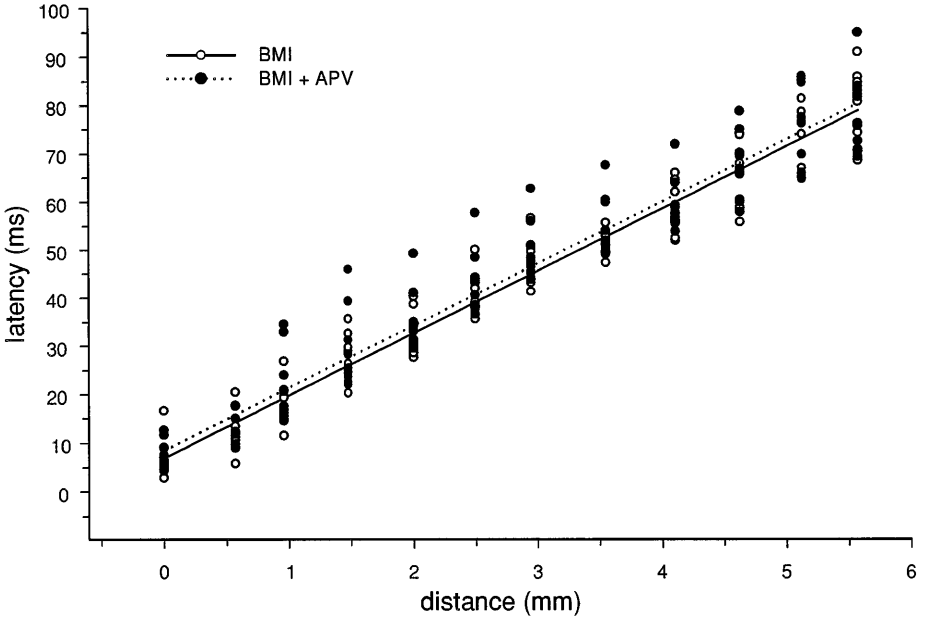

FIG. 2. Uniform propagation of stimulus-induced epileptiform activity in a sagittal neocortical slice analyzed at 12 recording sites. The stimulating electrode was located below first recording electrode at position 0 mm. The latency from stimulus to the field potential peak amplitude is plotted versus the distance from the first recording electrode. Epileptiform responses propagate continuously in rostro-caudal direction in BMI at 77.4 mm/s (○, R^2 = 0.95, n = 108) and in BMI + APV at 77.6 mm/s (●, R^2 = 0.92, n = 108).

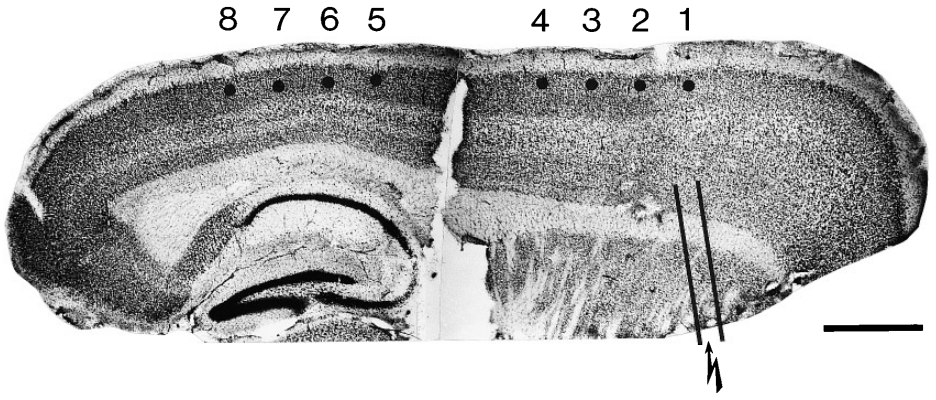

FIG. 3. Photograph of sagittal slice used for effect of vertical incision on intracortical spread of epileptiform responses. Location of the eight recording electrodes (●) and stimulation site in layer VI below electrode 1 is indicated. Slice was fixed and Nissl-stained for verification of cortical layers. Scale bar, 1 mm.

20–30% (Fig. 4B; filled bars in Fig. 4C). These data indicate that horizontal fibers located in layer I play an important role in transmitting epileptiform responses to remote cortical regions.

Action of Potential Anticonvulsants

Cromakalim (BRL 34915) is a potassium channel activator (2) with an anticonvulsant effect in an *in vitro* seizure model (3). At concentrations between 100 and 300 μM, cromakalim significantly reduced epileptiform activity in guinea pig hippocampal slices. Our results indicate that 300 μM cromakalim also completely blocks the spread of epileptiform responses in disinhibited rat neocortical slices (Figs. 5A, 5B). Cromakalim decreased the average relative field potential amplitude recorded at electrode position 1 from 100 to 6.9 ± 7.4% (n = 9, Fig. 5C). At recording electrode 2 the response was reduced from 92.3 ± 9.4 to 5.8 ± 6.2% (n = 9), indicating that cromakalim also diminished presumably monosynaptic responses near the site of stimulation.

Recent reports indicate that activation of the 5-HT_{1A} receptor decreases synaptic excitation (32) and inhibits epileptiform activity in CA1 hippocampal slices (31). Therefore the effect of the 5-HT_{1A} agonist 8-OH-DPAT on stimulus-evoked epileptiform responses was studied in disinhibited neocortical slices. Neither the spread nor the field potential response amplitudes were influenced by 30 μM bath-applied 8-OH-DPAT (Figs. 6A, 6B). The average relative response amplitude measured at the eight recording sites was either insignificantly reduced or enhanced, indicating that 5-HT_{1A} receptor activation in neocortical structures has no influence on the spread or magnitude of epileptiform activity.

Pattern and Pharmacology of Callosal Spread

The propagation of stimulus-evoked epileptiform responses to the contralateral hemisphere was studied in disinhibited coronal slices with intact corpus callosum. Under control conditions in normal bathing solution, electrical stimulation of the afferents below recording electrode 4 located medially in the ipsilateral hemisphere (↓ in Fig. 7A), elicited a field potential response at recording electrodes 4 and 3. No response could be observed under control conditions in the contralateral hemisphere (bottom four traces in Fig. 7A). After disinhibiting the slice with 20 μM BMI, the stimulus-evoked response propagated uniformly to the neighboring recording sites in the ipsilateral hemisphere (top four traces in Fig. 7B) and with a delay of 41.5 ± 7.2 ms (n = 16 slices) also to the corresponding representation in the contralateral hemisphere, from where it spread in lateral direction (bottom four traces in Fig. 7B). In agreement with our observations on the intrahemispheric spread, the interhemispheric propagation of epileptiform activity was also independent on NMDA receptor activation (Fig. 7C). Bath application of 30 μM APV did not affect the average field potential amplitudes recorded in the ipsi- or contralateral hemisphere (Fig. 7E). However, addition of 10 μM NBQX blocked all synaptic responses (Fig. 7D and filled columns in Fig. 7E).

DISCUSSION

The major results of the present *in vitro* studies in disinhibited mouse neocortical slices are: (i) The extensive intra- and interhemispheric spread of epileptiform activity shows a similar uniform propagation pattern with a velocity of ~0.08 m/s and the same sensitivity to antagonists acting at ionotropic glutamate receptors. Blockade of the NMDA receptor does neither significantly reduce the amplitude of the propagating epileptiform responses nor change the velocity of spread. Combined application of a NMDA and AMPA antagonist blocks all epileptiform activity. (ii) Layer I is sufficient to mediate the intracortical spread of epilepti-

form responses. (iii) The potassium channel opener cromakalim has a prominent anticonvulsant effect. (iv) Activation of potassium channels coupled to the 5-HT_{1A} receptor has no effect on the generation or propagation of epileptiform activity.

Propagation Pattern of Epileptiform Activity in Neocortical Structures

Stimulus-evoked epileptiform responses propagated uniformly within one hemisphere in medio-lateral and rostro-caudal direction. The velocity of spread observed in both directions (~0.08 m/s) is in good agreement with previous *in vitro* observations using the rat barrel cortex *in vivo* (~0.05 m/s) (5), the disinhibited guinea pig CA3 hippocampal preparation (0.13 m/s) (23), the low calcium/high magnesium model in CA1 rat hippocampal slices (0.04–0.12 m/s) (17), the low magnesium model in guinea pig neocortical slices (0.04 m/s) (39), and the low bicuculline model in the rat neocortex (~0.1 m/s) (8). We have no evidence for a nonuniform propagation of epileptiform activity as previously reported in rat somatosensory (11, 37) and cat visual (11) cortical slices. Although differences in the neocortical architecture between these species and the mouse may account for this discrepancy, it is more likely that the multielectrode array used in the present study does not show the necessary spatial resolution to resolve this phenomenon (≤200 μm) (11, 37).

A remarkable finding of the present study is the

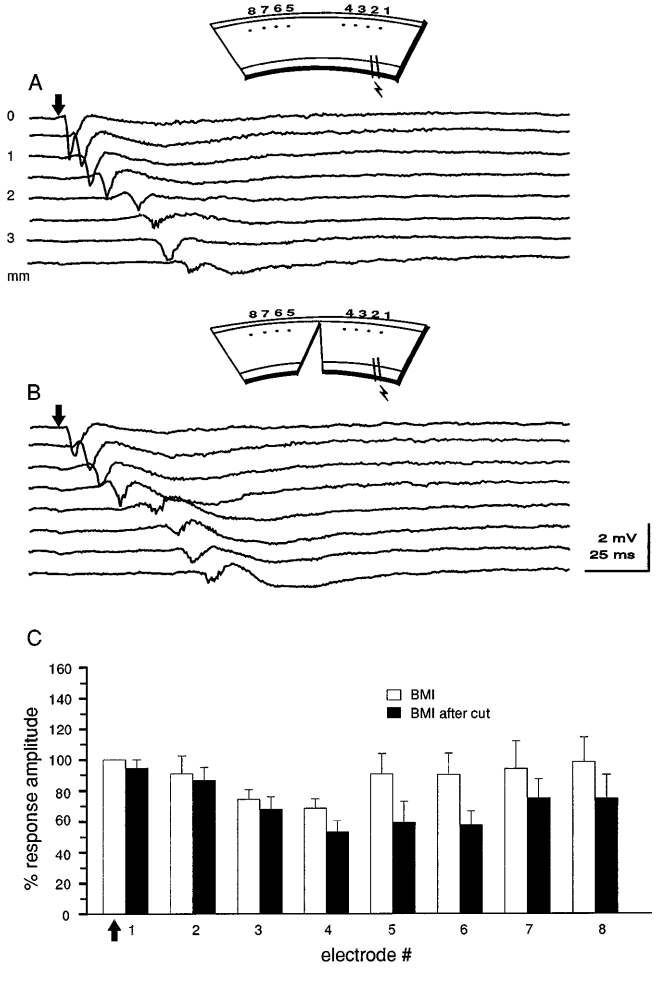

FIG. 4. Role of layer I in intracortical propagation of epileptiform activity in a sagittal slice. (A) Eight recording electrodes were positioned in supragranular layers and electrical stimulation was performed below first electrode (↓; see also schematic illustration). Stimulus-induced epileptiform responses propagate in the intact slice continuously in rostro-caudal direction. (B) After inducing a vertical incision in the slice, which leaves only layer I intact (see Fig. 3), propagating epileptiform responses could be recorded at all sites. (C) Quantitative results on the effect of a vertical incision on propagation pattern in BMI (n = 9). Data were obtained in intact slice as shown in A (open bars) and after vertical incision as illustrated in B (filled bars).

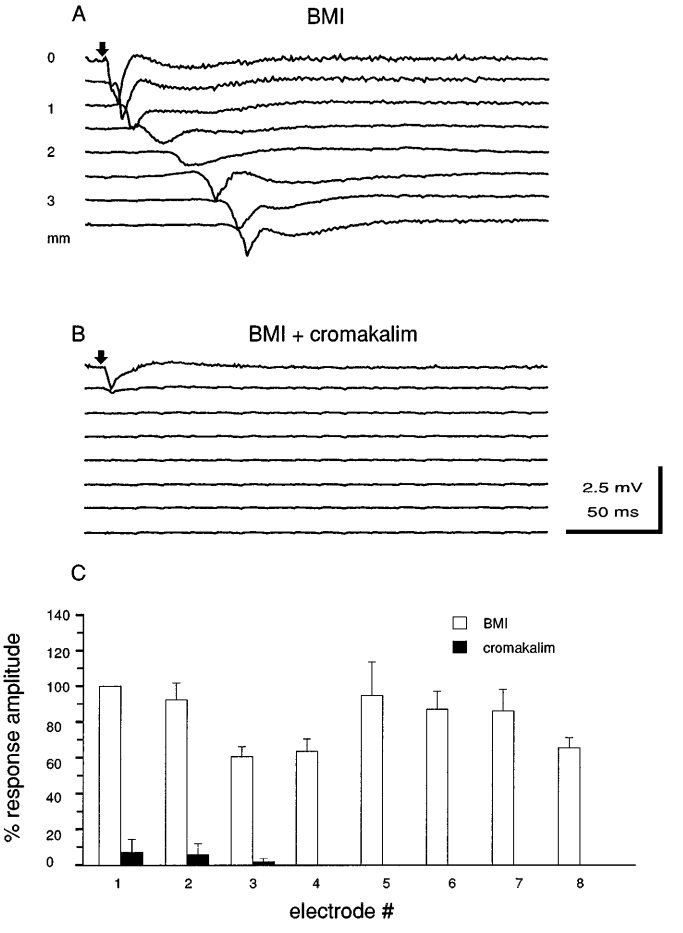

FIG. 5. Intracortical propagation of epileptiform activity is blocked by the potassium channel opener cromakalim. (A) Spread of stimulus-induced field potential responses in 20 μM BMI in a coronal cortical slice. Stimulation site at first electrode is marked by ↓. (B) Bath application of 300 μM cromakalim blocks the spread of epileptiform activity. (C) Quantitative results on the relative field potential response amplitude in BMI (open bars) and after addition of 300 μM cromakalim (filled bars) (n = 9).

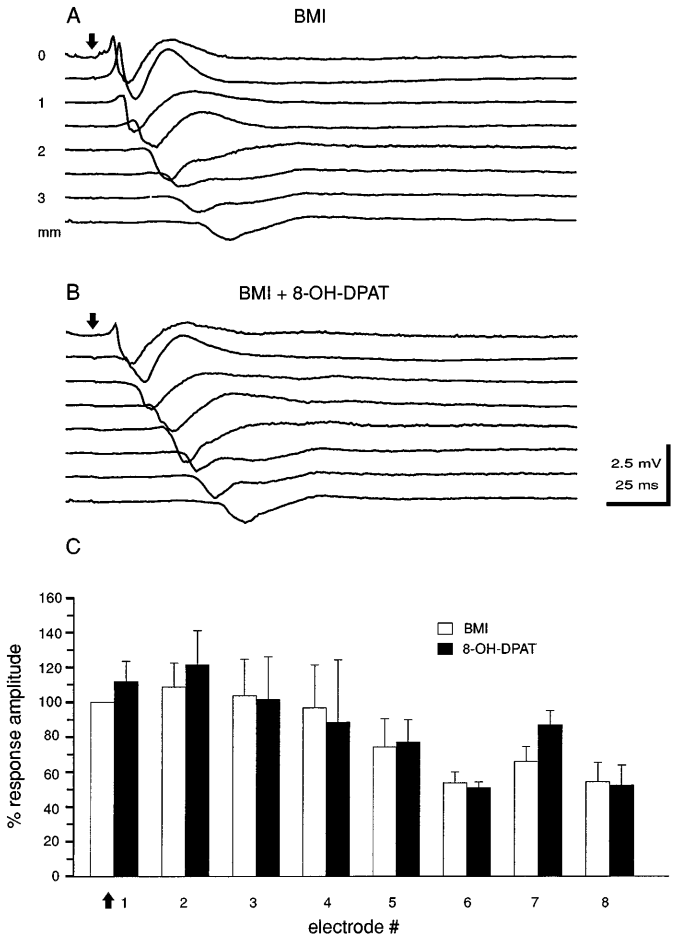

FIG. 6. Effect of 5-HT_{1A} receptor activation on stimulus-evoked epileptiform responses in coronal cortical slice. (A) Responses recorded in 20 μM BMI upon stimulation below first recording electrode (↓). (B) Same as in A, but after addition of 30 μM 8-OH-DPAT. (C) Normalized field potential response amplitudes in BMI (open bars) and after addition of 8-OH-DPAT (filled bars) ($n = 7$).

observation that the spread of stimulus-evoked epileptiform responses was not prevented by a vertical incision leaving only layer I intact. Previous studies in guinea pig neocortical slices have already shown that layers I–III play an important role in the propagation of epileptiform activity (1). Chervin *et al.* (11) and Albowitz and Kuhnt (1) suggested that this spread may be mediated by supragranular long-range horizontal connections (25, 26). Our data indicate that horizontal fibers in layer I are clearly involved in the transfer of synchronized epileptiform activity to remote cortical regions. This result is in good agreement with anatomical and *in vitro* electrophysiological observations by Cauller and Connors (7), who demonstrated in layer I a monosynaptic glutamatergic input onto the distal apical dendrites of layers II, III, and V pyramidal neurons. Since only a subpopulation of layer V pyramidal cells, the so-called intrinsic bursting neurons, show an extensive dendritic arborization in layer I (10), and because these cells probably play a major role in the generation (12) and propagation (9) of epileptiform activity in neocortical structures, the input in layer I on the distal apical dendrite of layer V bursting neurons may promote epileptiform responses under conditions of intracortical disinhibition. The sources of this input are probably thalamocortical and reciprocal corticocortical afferents (7).

Role of Ionotropic Glutamate Receptors

The intra- and interhemispheric spread of stimulus-induced epileptiform activity was not significantly influenced by APV, indicating that NMDA receptors play a minor role in the propagation process. This result is in good agreement with previous observations in rat neocortical slices (20), in rat primary motor cortex *in vivo* (6) and in the guinea pig whole brain preparation (13) when the $GABA_A$ receptor is blocked by bicuculline methiodide or picrotoxin. In disinhibited CA3 hippocampal slices, NMDA receptor application did also not prevent the spread of stimulus-evoked or spontaneous epileptiform activity, but slowed the propagation velocity from ~0.2 to ~0.1 m/s (36). Our data on the influence of APV on the spread of epileptiform responses indicate that NMDA receptors do not significantly contribute to the propagation velocity in disinhibited neocortical slices. In contrast, application of the specific AMPA receptor antagonist NBQX completely blocked the generation and intracortical and callosal spread of epileptiform responses. This result is in good agreement with previous *in vivo* and *in vitro* observations in the rodent cortex (6, 13, 20). In rat motor cortical slices with intact GABAergic inhibition, Hess *et al.* (19) observed a small APV-sensitive component in horizontal and oblique intracortical pathways. However, this component contributed only by 11% to the peak amplitude of the field potential response. Our observations are also in good correspondence with recent experimental and computational studies by Golomb and Amitai in disinhibited neocortical slices, which demonstrated that the propagation of epileptiform activity depended on activation of AMPA, but not NMDA receptors (15). Although AMPA receptor antagonists may be most beneficial as anticonvulsants (29, 30), their prominent influence on normal synaptic transmission hinder their clinical application.

An interhemispheric spread across the corpus callosum could be only observed when the slices were disinhibited by $GABA_A$ receptor blockade. Under these conditions, the callosal spread was dependent on AMPA receptors. This result is in agreement with previous intracellular observations by Kawaguchi (22), demonstrating an AMPA receptor-mediated excitatory commissural input.

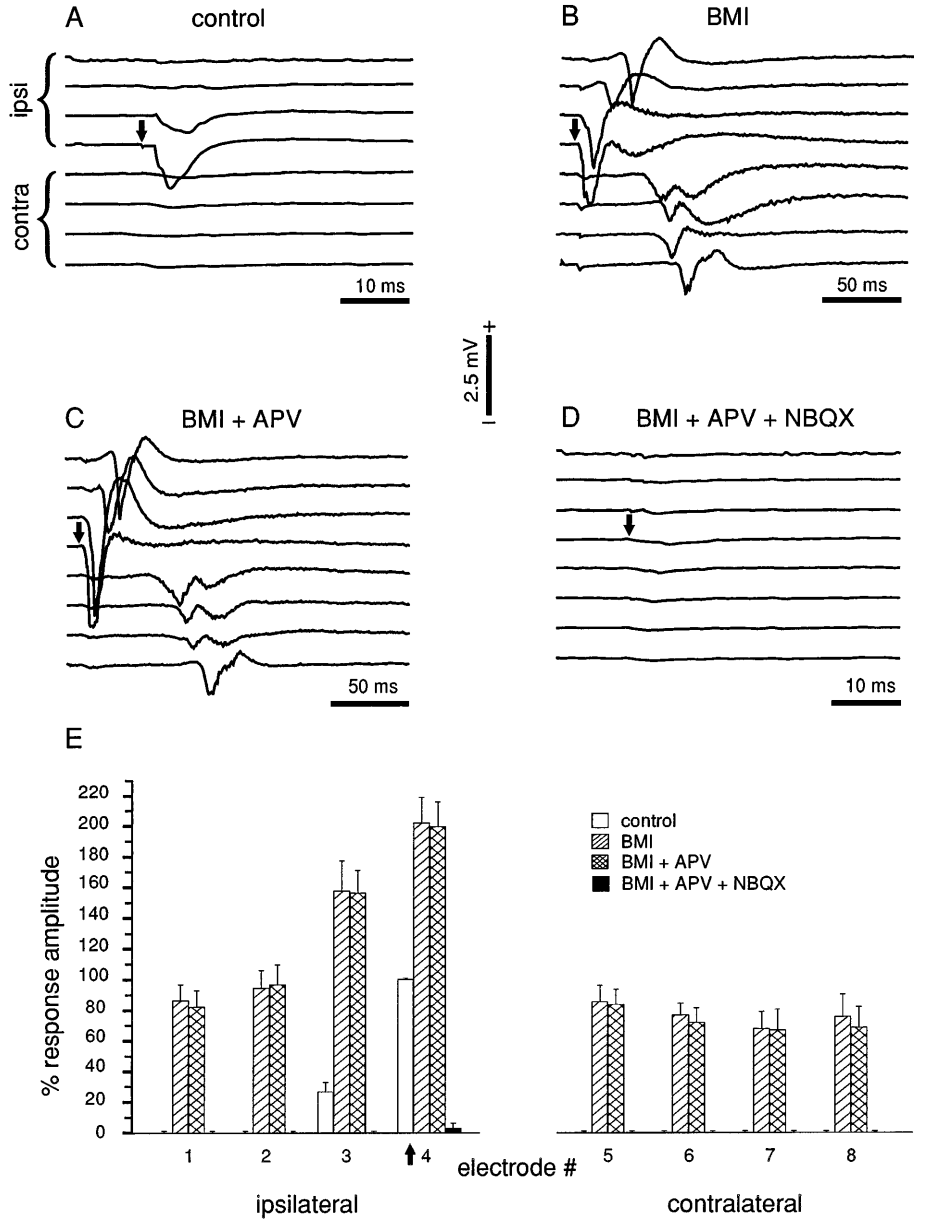

FIG. 7. Spread and pharmacology of BMI-induced epileptiform activity to the contralateral cortex. (A) Stimulus-induced field potential responses recorded in the ipsilateral (top 4 traces) and contralateral (bottom 4 traces) cortex to stimulation of tissue below fourth electrode (↓). Note spread of response to neighboring recording site in the ipsilateral cortex, but not to the contralateral hemisphere. (B) Addition of 20 μM BMI causes enhanced ipsilateral spread and propagation of epileptiform responses to contralateral cortex at electrodes 5 to 8. (C) Bath application of 30 μM APV does not influence the spread of activity in the ipsi- or contralateral cortex. (D) Addition of 10 μM NBQX blocks all stimulus-induced responses. (E) Quantitative results on the effects of BMI, APV, and NBQX (see inset) on stimulus-induced field potential responses in a coronal cortical slice with intact corpus callosum ($n = 16$).

Role of Potassium Channels in Controlling Spread of Epileptiform Activity

As previously reported by Alzheimer and ten Bruggencate (3) for different *in vitro* hippocampal epilepsy models, the smooth muscle relaxant cromakalim also blocked epileptiform activity in disinhibited neocortical slices. This anticonvulsant action of cromakalim probably results from a hyperpolarization of the membrane potential due to the activation of an inwardly rectifying potassium conductance (2). Furthermore, cromakalim may facilitate calcium-dependent potassium conductances and thereby enhance the slow afterhyperpolarization (2). Both mechanisms decrease the excitability of the neuronal network and have a strong anticonvulsant action. Although serotonin may have very similar effects (e.g., activation of an inwardly rectifying potas-

sium conductance) (38), the expression and propagation of epileptiform activity in the disinhibited neocortical slice was not significantly influenced by activation of the 5-HT_{1A} receptor. This result is in contrast to previous intracellular measurements in CA1 hippocampal neurons by Salgado and Alkadhi (31), who reported a prominent reduction of bicuculline-induced epileptiform activity by 8-OH-DPAT (20 μM). In CA1 neurons, this 5-HT_{1A} effect is probably mediated by an opening of a potassium channel (4) and a reduction of presynaptic calcium entry, which subsequently decreases glutamatergic synaptic transmission (32). Obviously, this mechanism in the disinhibited mouse neocortical slice is insufficient to reduce epileptiform activity. RNAse mapping and *in situ* hybridization studies in the rat forebrain have shown that the 5-HT_{1A} mRNA and protein is expressed much more strongly in the CA1 region than in the neocortex (28). Under the assumption that similar regional variations also exist in the mouse forebrain, it can be expected that 8-OH-DPAT has different effects on epileptiform activity in CA1 versus neocortical areas.

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