Kindling Induces Transient NMDA Receptor–Mediated Facilitation of High-Frequency Input in the Rat Dentate Gyrus

JOACHIM BEHR,1 UWE HEINEMANN,2 AND ISTVAN MODY1
1Departments of Neurology and Physiology, Reed Neurological Research Center, UCLA School of Medicine, Los Angeles, California 90095-1769; and 2Johannes-Mueller Institute of Physiology, Humboldt University Berlin, 10117 Berlin, Germany

Received 12 June 2000; accepted in final form 4 January 2001

Behr, Joachim, Uwe Heinemann, and Istvan Mody. Kindling induces transient NMDA receptor–mediated facilitation of high-frequency input in the rat dentate gyrus. J Neurophysiol 85: 2195–2202, 2001. To elucidate the gating mechanism of the epileptic dentate gyrus on seizure-like input, we investigated dentate gyrus field potentials and granule cell excitatory postsynaptic potentials (EPSPs) following high-frequency stimulation (10–100 Hz) of the lateral perforant path in an experimental model of temporal lobe epilepsy (i.e., kindled rats). Although control slices showed steady EPSP depression at frequencies greater than 20 Hz, slices taken from animals 48 h after the last seizure presented pronounced EPSP facilitation at 50 and 100 Hz, followed by steady depression. However, 28 days after kindling, the EPSP facilitation was no longer detectable. Using the specific N-methyl-D-aspartate (NMDA) and RS-α-amino-3-hydroxy-5-methyl-4-isoxazoleproponic acid (AMPA) receptor antagonists 2-amino-3-phosphonovaleric acid and SYM 2206, we examined the time course of alterations in glutamate receptor–dependent synaptic currents that parallel transient EPSP facilitation. Forty-eight hours after kindling, the fractional AMPA and NMDA receptor–mediated excitatory postsynaptic current (EPSC) components shifted dramatically in favor of the NMDA receptor–mediated response. Four weeks after kindling, however, AMPA and NMDA receptor–mediated EPSCs reverted to control-like values. Although the granule cells of the dentate gyrus contain mRNA-encoding kainate receptors, neither single nor repetitive perforant path stimuli evoked kainate receptor–mediated EPSCs in control or in kindled rats. The enhanced excitability of the kindled dentate gyrus 48 h after the last seizure, as well as the breakdown of its gating function, appear to result from transiently enhanced NMDA receptor activation that provides significantly slower EPSC kinetics than those observed in control slices and in slices from kindled animals with a 28-day seizure-free interval. Therefore, NMDA receptors seem to play a critical role in the acute throughput of seizure activity and in the induction of the kindled state but not in the persistence of enhanced seizure susceptibility.

INTRODUCTION

Repetitive high-frequency stimulation (kindling) of various brain regions results in the progressive development of seizure activity (Goddard et al. 1969; Racine 1972) whereby initially sub-convulsive stimulation leads to the gradual development of generalized seizures. This permanently enhanced excitability is thought to result from changes both at the cellular and at the network level (McNamara 1994, 1995; Mody 1993). Because both N-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptor antagonists delay the induction of kindling (Bowyer 1982; Cain et al. 1988; Croucher et al. 1988; Dennison and Cain 1989; Holmes et al. 1990; McNamara 1989; Peterson et al. 1983, 1984; Sato et al. 1988), glutamatergic neurotransmission is critically involved in the generation of kindling epilepsy. Indeed, alterations in excitatory synaptic transmission were described in human (Isokawa and Lévesque 1991; Represa et al. 1989) and in experimental animal models of epilepsy (McNamara 1995; Mody 1998). The entorhinal cortex provides the main input to the hippocampus (Witter 1993) and seems to be involved in temporal lobe epilepsy (Collins et al. 1983; Dasheiff and McNamara 1982; Rutecki et al. 1989; Spencer and Spencer 1994). It has been suggested that the dentate gyrus functions as a filter that prevents the spread of seizure activity to the hippocampus (Alger and Teyler 1976; Heinemann et al. 1992; Lothman et al. 1992; McNaughton et al. 1981). This gating mechanism breaks down after chronic epilepsy is induced by kindling that facilitates the propagation of epileptiform activity (Behr et al. 1996, 1998). Single cellular and neuronal network alterations both may be responsible for loss of filter function (Ribak et al. 1992; Schwartzkroin 1993). At the network level, mossy fiber sprouting appears to result in long-term structural alterations that may facilitate dentate gyrus throughput (Cronin and Dudek 1988; Dudek and Spitz 1997; Golarai and Sutula 1996; McNamara 1994; Patrylo and Dudek 1998; Wuarin and Dudek 1996). Previous studies described changes in the glutamatergic system at the cellular level that led to an increase in excitability that facilitated synaptic transfer from the entorhinal cortex to the hippocampus (Köhr and Mody 1994; Köhr et al. 1993; McNamara 1994, 1995; Mody and Heinemann 1987; Mody and Lieberman 1998; Mody et al. 1988). However, the long-term contribution of this increase in excitability to the breakdown of the dentate gyrus gating mechanism is unclear. In this study we investigate acute and persistent alterations of glutamate receptor–mediated excitatory postsynaptic potentials (EPSPs) and currents (EPSCs) in the dentate gyrus and their role in the integration of high-frequency input from the entorhinal cortex.
METHODS

Kindling

Experiments were performed in 31 control hippocampal horizontal slices, obtained from seven age-matched unimplanted controls and six sham-implanted controls, and 42 kindled hippocampal slices taken from 15 fully kindled 450–600 g adult Wistar rats. Animals were stimulated until ≥15 consecutive stage 5 seizures were obtained. In an attempt to differentiate acute and enduring changes of synaptic transmission after kindling, kindled rats were used 48 h (n = 8) or 28 days (n = 7) after the last stimulus induced a stage 5 seizure. Bipolar stainless steel electrodes were implanted under Na-pentobarbital anesthesia (75 mg/kg i.p.) into the left amygdala (relative to bregma in mm: −2.5 posterior; 5 lateral; 8.5 below cortex) (Paxinos and Watson 1986). After a postsurgical recovery period of 7–8 days, animals were stimulated daily through the implanted electrode with a train of biphasic 150 μA pulses at 60 Hz for 1 s. Behavioral changes during kindling were scored according to the scale of Racine (1972).

Slice preparation and solutions

At the indicated times after the last seizure, the rats were decapitated under deep ether anesthesia, their brains were quickly removed, and 400-μm-thick slices were prepared with a Campden Vibroslicer (Campden, Loughborough, UK). The slices were transferred to an interface recording chamber that was continuously perfused with aerated (95% O2 -5% CO2), prewarmed (34°C) artificial cerebrospinal fluid (ACSF) containing (in mM) 124 NaCl, 1.25 NaH2PO4, 26 NaHCO3, 3 KCl, 1.6 CaCl2, 1.8 MgSO4, and 10 glucose, pH 7.4. For all experiments on EPSCs, the CaCl2 and MgCl2 concentrations were increased to 4 mM and 50 μM picrotoxin was present.

Recording and data acquisition

Field potentials (fEPSPs), EPSPs, and EPSCs were evoked using 100-μs pulses every 10 s. These pulses were delivered through bipolar electrodes that were placed in the outer third of the molecular layer of the upper blade of the dentate gyrus to preferentially stimulate lateral perforant path fibers. Stimulus intensity was adjusted to 50–70% of maximum response. Selective recordings of EPSPs and EPSCs at lateral perforant path synapses were by determining the effect of paired-pulse stimulation on EPSPs (Macek et al. 1996; McNaughton 1980). Recordings exhibiting paired pulse depression at an interstimulus interval of 100 ms were rejected. Field potentials were recorded with ACSF-filled microelectrodes. For voltage-clamp recordings with sharp microelectrodes (40–50 MΩ resistance) filled with 2.5 M K-acetate and 50 mM QX 314, a SEC10L amplifier (NPI Instruments, Tamm, Germany) in discontinuous single electrode voltage-clamp mode was employed to eliminate access resistance artifacts. Neurons were voltage-clamped at −60 mV for recordings of evoked EPSCs. Recorded fEPSPs, EPSPs, and EPSCs were filtered at 3 kHz, sampled at 10 kHz, and collected using a TIDA interface (HEKA, Lambrecht/Pfalz, Germany). Peak amplitudes of fEPSPs and EPSCs were measured from the averages of 8–10 sweeps. Population spikes were calculated as the mean amplitude of the negative and positive phases. Paired pulse facilitation and depression were expressed as the ratio of the peak amplitude of the second fEPSP to the peak amplitude of the first fEPSP. In recordings where the first fEPSP was followed by a field response contaminated by a population spike, the mean of the negative and positive phases was added to the underlying fEPSP. This procedure underestimates the underlying fEPSP and produces a paired pulse facilitation that is smaller than or equal to the real ratio. To more accurately quantify these differences, we turned to intracellular and voltage clamp recordings in the presence of a sodium channel blocker. EPSC charges were calculated by integrating the traces. Statistical evaluation was performed by applying student’s t-test (Origin 4.1, Microcal); data are expressed as means ± SE. Significance level was set to P < 0.05.

Drugs

The following drugs were bath applied: 2-amino-5-phosphonovaleric acid (APV) (Research Biochemicals, Natick, MA), 6-nitro-7-sulphamoylbenzo(f)quinoxaline-2,3-dione (a gift from Novo Nordisk, Denmark), SYM 2206 (Tocris, Bristol, UK), and picrotoxin (Fluka BioChemika, Ronkonkoma, NY).

RESULTS

Using extracellular field potential recordings, we investigated the network behavior of the epileptic dentate gyrus following high-frequency stimulation (10 pulses at 100 Hz) of the lateral perforant path. In control slices, repetitive stimulation of perforant path fibers resulted in steady fEPSP depression (n = 6) (Fig. 1A). In contrast, 48 h after kindling, kindled slices (n = 6) showed a pronounced facilitation of the second, and occasionally of the third pulse, which was also followed by fEPSP depression (n = 6). Interestingly, 28 days after the last seizure, the discharge pattern reverted to control conditions (n = 8). These slices showed a steady depression of fEPSPs and lacked the strong facilitation that was observed in kindled slices 48 h after the last seizure. Analysis of the frequency dependence of the paired pulse ratios (pulse 10 relative to pulse 1) for each individual animal group revealed significant fEPSP depression at frequencies greater than 20 Hz in all experimental groups (Fig. 1B). It is noteworthy that application of the GABAA and GABA B receptor antagonists bicuculline (5 μM) and CGP 55845A (2 μM) to control slices (n = 3) did not prevent steady depression of fEPSPs; it is therefore unlikely that GABAergic mechanisms were involved (data not shown).

To determine the frequency necessary to induce fEPSP facilitation in animals dissected 48 h after kindling, we conducted paired pulse protocols at 10, 20, 50, and 100 Hz (Fig. 2, A and B). Although control slices and slices 28 days after kindling showed a paired pulse depression at 50 and 100 Hz, slices from animals 48 h after the last seizure presented strong paired pulse facilitation. At 100 Hz, the paired pulse ratio (pulse 2 relative to pulse 1) significantly increased from 0.75 ± 0.04 (n = 6) in controls to 3.45 ± 0.88 (n = 6) in kindled slices prepared 48 h after the last seizure. The value dropped, however, to 0.60 ± 0.02 (n = 8) in slices examined 28 days after kindling. Application of the NMDA receptor antagonist APV (60 μM) completely blocked paired pulse facilitation in kindled slices (48 h after kindling), which resulted in a paired pulse ratio of 0.82 ± 0.12 (n = 4) that was not significantly different from control slices recorded in the presence of APV (0.80 ± 0.02, n = 3) (Fig. 2C).

To elucidate the mechanism underlying fEPSP facilitation, simultaneous field potential and intracellular current clamp recordings were performed during paired pulse stimulation in control slices (n = 3 cells) and in kindled slices 48 h after the last seizure (n = 3 cells). Although cells in control slices showed a paired pulse depression similar to that obtained by field potential recordings, cells in kindled slices typically presented an action potential on the second stimulus (at 50 and 100 Hz) that contributed to the facilitated population spike in field potential recordings (Fig. 3Aa). Superimposing the representative normalized traces of both experimental groups re-
To quantify acute and long-lasting changes in the contributions of NMDA, RS-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate (KA) receptor–mediated EPSCs to the control response, we successively applied the NMDA receptor antagonists APV (60 μM) and the potent AMPA receptor antagonist SYM 2206 (100 μM) (Li et al. 1999; Rodríguez-Moreno et al. 2000) to the different experimental groups (Fig. 4A). In control slices, application of APV and SYM 2206 blocked single stimulus–evoked non-NMDA receptor–mediated responses, which indicated that postsynaptic KA receptor activation was lacking (n = 4). Because KA EPSCs facilitate during high-frequency stimulation of mossy fibers in CA3 neurons (Castillo et al. 1997; Vignes and Collingridge 1997), we applied trains of stimuli between 50 and 500 Hz to perforant path fibers to test whether KA receptor–mediated EPSCs of dentate gyrus cells behave in a similar fashion. However, in contrast to CA3 pyramidal cells, repetitive stimulation of granule cells did not result in the facilitation of KA receptor–mediated EPSCs (n = 4). The same results were obtained in kindled preparations. We could not record SYM 2206–resistant kainate receptor–mediated currents either 48 h (n = 3) or 28 days (n = 3) after kindling (data not shown). Therefore, both in control and in epileptic rat dentate gyri, the non-NMDA receptor–mediated responses seem to be caused solely by AMPA receptor activation.

By normalizing the charge and the amplitude of control responses consisting of NMDA and AMPA receptor–mediated components, we calculated the fraction of APV-insensitive inward currents in control and in kindled preparations (Fig. 4B). In kindled rats 48 h after the last stimulation, the fraction both of the amplitude (0.46 ± 0.06, n = 9, P < 0.05) and of the charge (0.39 ± 0.06, n = 8, P < 0.05) of APV-resistant, AMPA receptor–mediated EPSCs was significantly decreased compared with the control group (0.79 ± 0.04, n = 11, and 0.69 ± 0.03, n = 11, respectively). However, four weeks after the last seizure in kindled animals, the amplitude and charge fractions of AMPA receptor–mediated EPSCs were control-like (0.72 ± 0.06, n = 10, and 0.80 ± 0.04, n = 5, respectively). In control slices and in kindled slices 28 days after the last seizure, inclusion of APV (60 μM) did not significantly change EPSC decay time (9.8 ± 1.9 and 9.8 ± 0.7 ms), most likely because, in the presence of 4 mM Mg2+ at −60 mV holding potential, most of the NMDA receptors are already blocked under control conditions. However, in kindled slices 48 h after the last seizure, the prominent APV-induced decrease in amplitude was paralleled by a significant decrease in decay time (11.6 ± 1.0 ms, P = 0.001). This finding agrees with the altered Mg2+ blockage reported in the kindled dentate gyrus (Köhr et al. 1993).

By subtracting the APV-resistant EPSC amplitudes and charges from their normalized control values, we calculated the values for the NMDA receptor–mediated component. The fraction of NMDA receptor–mediated EPSCs shows a dramatic increase in its amplitude, from 0.21 ± 0.04 (n = 17) to 0.54 ± 0.06 (n = 9) (P < 0.05), as well as in its charge, from 0.30 ± 0.03 (n = 11) to 0.61 ± 0.06 (n = 8) (P < 0.05), 48 h after the last seizure. However, four weeks after the last seizure, the amplitude and charge fractions of the isolated NMDA compo-
DISCUSSION

Using high-frequency stimulation of lateral perforant path fibers, we demonstrated a transient facilitation of field and single-cell EPSPs in the kindled dentate gyri recorded 48 h after the last seizure. In contrast, the discharge patterns in control and in kindled animals dissected 28 days after the last seizure failed to show any facilitation and were characterized by a steady depression. The facilitation in acutely kindled preparations most likely results from transiently enhanced NMDA receptor–mediated current that provides a significantly slower EPSC kinetic than do control slices and kindled slices from animals with a 28-day seizure-free interval.

The dentate gyrus plays a crucial role in the propagation of seizures from the entorhinal cortex to the hippocampus. In the entorhinal cortices of KA-treated rats and human epileptic brains, high-frequency oscillations (100–500 Hz) may contribute to the excitatory synaptic input to dentate granule cells (Bragin et al. 1999a,b). Seizure-like events in the dentate gyri of KA-treated epileptic rats are characterized by synchronized field EPSPs that underscore the clustering of action-potential firing and that shift in their bursting patterns from fast and regular discharges (tonic phase) to slower and clustered discharges (clonic phase) with frequencies from 1 to 100 Hz (Wuarin and Dudek 1996). Also, in in-vitro models of epilepsy, stimulus-evoked and spontaneous synchronous population spikes with frequencies of up to 300 Hz were observed (Schweitzer et al. 1992). Accordingly, sustained stimulation at 10–100 Hz partially models the synaptic input to the dentate gyrus that occurs during the initial tonic and subsequent clonic phases of dentate gyrus seizure activity. Facilitation of fEPSPs only occurred within the initial 50 ms of a train of evoked responses and was succeeded by steady depression. Because the tonic phase of epileptiform activity generally lasts for a few seconds with a frequency of more than 10 Hz, our results suggest that facilitation of tonic epileptiform discharges is rapidly followed by efficient depression. Therefore, kindling induces a short-lasting throughput of high-frequency input that may propagate to the hippocampus. This facilitation of high-frequency input in kindled animals is consistent with the enhanced excitability of the kindled dentate gyrus, which may no longer function as a filter that prevents the spread of epileptiform activity from the entorhinal cortex to the hippocampus (Behr et al. 1998; Heinemann et al. 1992; Lothman et al. 1992). Because bath application of GABAA and GABAB antagonists could not prevent the depressive effect, activation of GABAergic inhibition does not seem to be critically involved in this phenomenon. Postsynaptic receptor desensitization could be involved in frequency-dependent depression under some conditions (Larkman et al. 1997; Takahashi et al. 1995). However, because the enhanced transmitter release caused by sustained stimulation results in depletion of presynaptic glutamate vesicles, a presynaptic mechanism most likely accounts for the observed effect (Galarreta and Hestrin 1998; Liu and Tsien 1995; Ryan and Smith 1995; Silver et al. 1998; Zucker 1989).

The present study demonstrates a pronounced increase in the

![Figure 2](http://jn.physiology.org/)

**FIG. 2.** Frequency dependence of field excitatory postsynaptic potential (EPSP) facilitation in control and in kindled rats. A: paired pulse stimulation at 20, 50, and 100 Hz in control and in kindled rats (48 h and 28 days after kindling). Although control slices and slices 28 days after kindling showed paired pulse depression at 50 and 100 Hz, slices from animals 48 h after the last seizure presented significant paired pulse facilitation (arrows). The N-methyl-D-aspartate (NMDA) receptor antagonist 2-amino-5-phosphonovaleric acid (APV) (60 μM) completely blocked EPSP facilitation in kindled slices, resulting in a paired pulse ratio not significantly different from control slices (C). B: frequency dependence of the averaged paired pulse ratios (pulse 2 relative to pulse 1) for each animal group (solid line, control; dotted line, 48 h after kindling; dashed line, 28 days after kindling). Only in kindled animals, 48 h after the last seizure, did we record a significant paired pulse facilitation at 50 and at 100 Hz.
fraction of NMDA receptor–mediated EPSC (both in charge and in amplitude) 48 h after the last seizure of kindled rats whereas the fraction of the AMPA receptor–mediated EPSC component decreased significantly. However, this scenario changed 28 days after the last kindled seizure when the initially increased AMPA and NMDA components reverted to control-like values. Surprisingly, neither in control nor in kindled animals were postsynaptic KA receptor–mediated EPSCs recorded. APV-sensitive EPSP facilitation appears to result from transiently increased NMDA receptor–mediated current. Our results demonstrate, in kindled rats dissected 48 h after the last seizure, that EPSC decay time outlasts the time between two succeeding stimuli applied at frequencies greater than 20 Hz. Accordingly, NMDA receptor channels are not completely blocked when the second pulse is given. Considering the altered Mg²⁺ blockage reported in the kindled dentate gyrus (Koehr et al. 1993), NMDA receptor–mediated facilitation is feasible. The kindling-induced enhancement of NMDA receptor–mediated synaptic responses in dentate gyrus cells has been extensively studied (McNamara 1994, 1995; Mody and Heinemann 1987; Mody et al. 1988). Kindled granule cells exhibit voltage-dependent EPSPs that are increased by depolarization and low Mg²⁺ concentration and are reduced by APV; this reflects a contribution of NMDA receptors to synaptic transmission in the kindled dentate gyrus (Mody et al. 1988). At the single-channel level, this enhanced NMDA function consists of prolonged openings of NMDA channels and an elevated phosphorylation state of the channel (Koehr et al. 1993). Activation of the phosphatase calcineurin is known to cause desensitization of NMDA receptors that results in the decrease of a succeeding stimulus-evoked NMDA receptor–mediated EPSC (Tong et al. 1995). Decreased calcineurin-mediated negative feedback on NMDA channels in the dentate gyrus of patients suffering from temporal lobe epilepsy and in those of kindled rats (Lieberman and Mody 2000; Mody and Lieberman 1998) may lead to the observed potentiation of the second NMDA receptor–mediated component. Therefore, we have to consider that seizure-induced alterations of the phosphorylation state of NMDA receptors caused by decreased calcineurin levels may cause changes in NMDA receptor function that may in turn exacerbate hyperexcitability. Even though NMDA channel openings are still prolonged when recorded 28 or 60 days after the last kindling stimulus (Mody and Lieberman 1998), initially enhanced NMDA receptor–mediated EPSCs declined to control levels after a period of 28 seizure-free days (Sayin et al. 1999). It is therefore possible that synaptic and extrasynaptic NMDA receptors are differentially regulated. The dentate gyrus seems to defend itself against long-term hyperexcitability during kindling, e.g., by lowering the initially increased density of postsynaptic NMDA receptors. Indeed, Kamphuis et al. (1995) found a significant increase of NR2B mRNA in the course of kindling and in fully kindled rats but, by 28 days after the last stimulation, the expression of NR2B had declined to control levels.

Few studies have addressed epilepsy-induced alterations of non-NMDA receptor–mediated neurotransmission in the dentate gyrus. Despite studies showing lasting increases of glutamate receptors mRNAs in the dentate gyri of patients suffering...
temporal lobe epilepsy (TLE) (Babb et al. 1996) as well as in two different animal models of TLE (Babb et al. 1996; Kamphuis et al. 1994; Pollard et al. 1993), the present study found no long-term increase of AMPA receptor–mediated EPSCs. This result, however, does not preclude somatic up-regulation of AMPA receptors.

In contrast to AMPA and NMDA receptors, the contribution of KA receptors to epileptogenesis has not been extensively investigated. Despite the potent epileptogenicity of KA administration (Ben-Ari 1985; Sperk 1994), we found no postsynaptic kainate receptor–mediated EPSCs either in control (Lerma et al. 1997) or in kindled animals. These results are at odds with the possible involvement of dentate gyrus kainate receptors in kindling epilepsy and are somewhat surprising because the dentate gyrus contains mRNA-encoding KA receptors (Kamphuis et al. 1995; Wisden and Seeburg 1993) that appear to be promising candidates for the mechanisms underlying the development and persistence of the kindled state. This result is like that obtained in area CA1, where pyramidal neurons express KA receptor subunits, but, as in the present study, it has been impossible to unmask synaptic currents mediated by KA receptors at the synapse established by Schaffer collaterals and pyramidal cells (Castillo et al. 1997; Frerking et al. 1998; Lerma et al. 1997). However, we cannot rule out either the presence of or the plastic changes of kainate receptors at other synapses, e.g., at granule cell to interneuron synapses, at the inhibitory terminals of interneurons, or at mossy cell to granule cell synapses.

A decrease in inhibition may also account for EPSP facilitation. This scenario appears to be unlikely, however, because blockage of fast and slow inhibition in control rats was not efficient in modeling the strong facilitation that was observed in kindled preparations. In addition, previous studies report a rather increased function of the GABAergic system after kindling (Buhl et al. 1996; Nusser et al. 1998) that may stem from increased excitatory input onto GABAergic neurons, from increased quantal size of inhibitory postsynaptic currents, and from reduced presynaptic autoinhibition of GABA release.

In addition to cellular alterations, there is some support for the hypothesis that feedback excitation by seizure-induced mossy fiber sprouting may lead to enhanced excitability and may facilitate dentate gyrus throughput (Cronin and Dudek 1988; Dudek and Spitz 1997; Golarai and Sutula 1996; McNamara 1994; Patrylo and Dudek 1998; Wuarin and Dudek 1996). However, an inhibitory rather than an excitatory function of the reorganized dentate gyrus also has been proposed (Ribak and Peterson 1991; Sloviter 1992). Alternatively, sprouting may not be a prerequisite of epilepsy because blockage of mossy fiber sprouting in two different models of TLE did not necessarily prevent the development of limbic seizures (Longo and Mello 1997, 1998).

In summary, the enhanced excitability of the kindled dentate gyrus 48 h after the last seizure, as well as the breakdown of its gating mechanism during high-frequency input, most likely is caused by increased NMDA receptor activation. Considering the transient nature of enhanced NMDA receptor activation, the critical role of this receptor seems to lie in the induction of structural and functional alterations induced by seizures (Can-
REFERENCES


BABBR TL, MATHERN GW, LEITE JP, PRETORIUS JK, YEOMAN KM, AND KUHL- CRONIN J AND D UDEK FE. Chronic seizures and collateral sprouting of dentate

CANTALLOPS I AND R OUTTENBERG A. Rapid induction by kainic acid of both

HEINEMANN U, BRICK H, DREIER JP, FICKER E, STAREL J, AND ZHANG CL. The dentate gyrus as a regulated gate for the propagation of epileptiform activity.


