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Epilepsy-Based Changes in Hippocampal Excitability: Causes and Effects

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INTRODUCTION

Pathophysiology of Temporal Lobe Epilepsy

Temporal lobe epilepsy (TLE) is characterized by spontaneously recurrent seizures (SRS) that originate from the temporal lobe (1). Electroencephalograms (EEG) will typically show interictal spikes and other abnormalities between seizures. The typical pathology is mesial temporal sclerosis (MTS) accompanied by mossy fiber sprouting (MFS) (2).

Chronic Seizure Models for Temporal Lobe Epilepsy

There are two main types of animal models of TLE, kindling and status epilepticus (SE). In the kindling model (3), spaced and repeated stimulations of the brain evoke afterdischarges (ADs) that increase progressively in duration and in the severity of clinical/ behavioral symptoms. Kindling allows good control of the timing of ADs, but a relatively large number of kindled ADs (>200) is required for SRS, irrespective of structures kindled. In contrast, SRS readily occur after a latent period of several weeks in a SE model (4,5). SE is commonly induced by a systemic injection of pilocarpine or kainic acid (KA) or by prolonged electrical brain stimulation. In addition, MTS and MFS are prominent after SE but not after kindling.

The main purpose of this chapter is to review the excitability changes in the hippocampus induced by TLE models. Excitability applies to different levels—the intrinsic neuronal membrane, neurons with excitatory and inhibitory synaptic inputs, and populations of interacting neurons. The working hypotheses are that seizures beget seizures *and* intractability and that understanding brain plasticity will help to ameliorate medical intractability.

CELLULAR AND SYNAPTIC CHANGES IN EXCITABILITY

Intrinsic Membrane Excitability

Kindling and SE have been shown to modify the voltage dependence of the Na^+ channels (6,7) and the response of the channel to anticonvulsants (8,9). After seizures, Na^+ channels open (activate) with a smaller depolarization from rest and they close (inactivate) at a more

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positive potential. These changes after seizures result in larger Na^+ currents near the resting potential. Conversely, anticonvulsants, such as carbamazepine, shift the Na^+ channel inactivation closer to resting potential and reduce channel opening. However, the latter anticonvulsant action is reduced in neurons derived from TLE models or from intractable TLE patients (8, but see 9).

Repeated action potentials (APs) or bursting, induced after kindling and SE (10,11), has long been considered a hallmark of "epileptic neurons." AP bursting may cause >200 Hz oscillations (ripples) in epileptic areas of humans and animals (12). Effective anticonvulsants typically suppress repetitive AP firing but not single APs. In part, anticonvulsants (such as phenytoin) may suppress bursting by suppressing a depolarizing afterpotential (DAP). The DAP in hippocampal CA1 neurons is mediated by a noninactivated Na^+ current and repolarized by various K^+ currents that include I_M (13) and Na^+-activated K^+ current (14).

Excitatory Transmission

N-methyl-D-aspartate (NMDA) receptor mediated responses in dentate gyrus (DG) granule cells (15,16) and CA3 (17) effectively increase for weeks after kindling or SE (18). In contrast, the iontropic, non-NMDA mediated glutamatergic excitation in the DG and CA1 is only increased during the early stage of kindling (19,20) or marginally after SE (18,21,22).

MFS has been suggested to increase the excitability of the hippocampus. Experiments in vitro showed that MFS correlated with an increase in recurrent excitation in the DG (23–25). However, in experiments on urethane-anesthetized rats, we were unable to show an increase in recurrent excitation in relation to MFS increase (21). Although SRS usually correlate with MFS in SE models, SRS still occurred when MFS and cell loss did not occur (26,27).

Inhibitory Transmission

$GABA_A$ receptors in DG were persistently altered following SE (28) and kindling (29). After seizures, mini or evoked $GABA_A$–mediated inhibitory postsynaptic currents (IPSC) were *increased* in DG granule cells (30). These IPSC in animals or TLE patients became more sensitive to blockade by Zn^{2+} and insensitive to BZ1-specific agonist zolpidem, possibly because of a relative decrease in $\alpha 1$ subunit expression (28).

Sloviter (31) proposed that GABAergic interneurons in TLE are functionally disconnected from their excitatory inputs ("dormant basket cells"), which may explain functional disinhibition despite a relative preservation of GABAergic neurons. However, specific types of interneurons may be lost as suggested by the differential loss of inhibition at dendritic and not somatic synapses (32,33; see Chapter 9). In addition, not all brain areas show inhibition loss, e.g., after TLE models, inhibition was decreased in CA1 and CA3 but not in DG (30,34–37) (Fig. 8-1B). A long-lasting decrease in $GABA_B$ receptor-mediated postsynaptic inhibition was shown in SE (38) but not after kindling (39). Decrease in $GABA_B$ presynaptic autoreceptor function was shown after both kindling (37) and SE (38).

Changes in Cellular Signaling

Knockout of the brain derived neurotrophic factor (BDNF) receptor TrkB (40) or NMDA receptor antagonists (41) has been shown to suppress epileptogenesis, as indicated by the progression of kindling. The duration of ADs evoked by amygdala stimulation in TrkB receptor knockout mice was not different from wild type mice but little progression in seizure severity was found in the knockout mice (41).

CHANGES IN NEURAL CIRCUITS

Alterations of Entorhinal-Hippocampal Circuitry After Kainic Acid SE

Studies of ion channels or single neurons in vitro do not necessarily predict events in the intact brain. Given that few studies have addressed the in vivo changes in multisynaptic neural circuitry after seizures, we studied the well-established

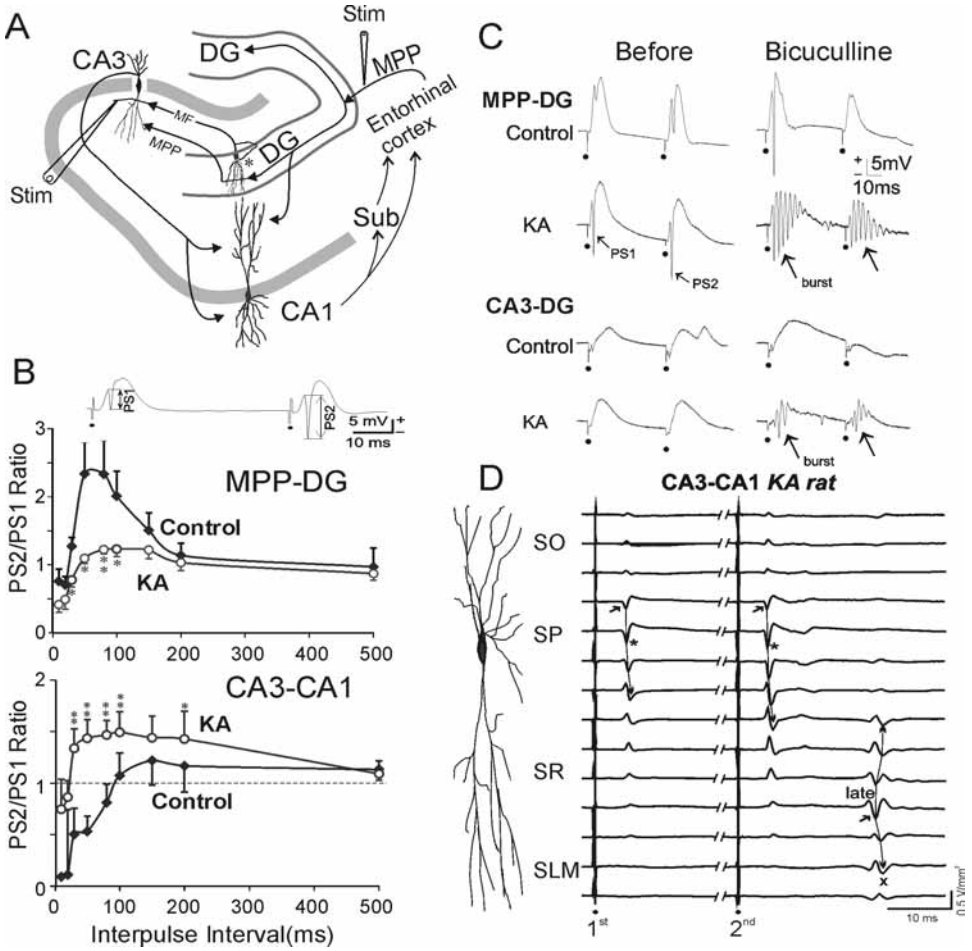

FIG. 8-1. Changes in the entorhinal cortex (EC)-hippocampal circuit after kainic acid (KA) or control treatment. **(A)** Schematic showing EC projects to dentate gyrus (DG), CA3 and CA1 through the medial perforant path (MPP). DG granule cells projects to CA3 through the mossy fibers (MF) which may show sprouting (*). CA3 pyramidal cells projects to CA1, which projects to EC, directly or indirectly via the subiculum (Sub). Stimulating electrodes (Stim) were placed in MPP and CA3b, and field potentials were recorded in CA1 and DG. **(B)** Paired-pulse response in the cell layer of DG (after MPP stimulation) and CA1 (after CA3 stimulation); stimulus artifact indicated by dots underneath traces. The ratio of the population spike evoked by the second pulse (PS2) to that evoked by the first pulse (PS1) is shown as a function of interpulse interval (IPI) in KA and control rats. Paired-pulse facilitation in CA1 and paired-pulse depression in DG are shown in KA-treated as compared to control rats (group difference, * $P<0.05$, ** $P< 0.01$). **(C)** Evoked field potentials of representative rats recorded at the DG granule cell layer, before and after injecting $GABA_A$ receptor antagonist bicuculline (7.5 nmol) intracerebroventricularly. Control rat showed paired-pulse depression after bicuculline while KA-treated rat showed bursting *(arrow)*, with MPP or CA3 stimulation. **(D)** Depth profile of the current source density in CA1 after paired-pulse (50 ms IPI) CA3 stimulation in a KA-treated rat. The first pulse or second pulse evoked an early population spike (*) that started in stratum oriens (SO) near stratum pyramidale (SP) and propagated to stratum radiatum (SR). A population spike of approximately 20 ms latency (labeled "late") was initiated by the second pulse at distal SR *(arrow)* and propagated proximally and distally to stratum lacunosum-moleculare (SLM). (Adapted from Wu K, Leung LS. In "Intractable Epilepsies", Blume WT et al. (Ed.), Lippincott, Adv Neurol 97: 63-68 Enhanced but fragile inhibition in the dentate gyrus in vivo in the kainic acid model of temporal lobe epilepsy—a study using current source density analysis. Neuroscience 2001;104:379 – 396, with permission from Elsevier.)

entorhinal cortex (EC)- hippocampus circuit (Fig. 8-1A) in urethane-anesthetized rats, 2 to 4 months after SE induced by KA (21,22).

Excitation in DG via the medial perforant path (MPP) was enhanced in KA-treated animals. The population spikes (synchronous extracellular action potentials) evoked by the first and second stimulus to the MPP were measured as PS1 and PS2 respectively (Fig. 8-1B). PS1 was increased greatly, but PS2 was only marginally increased in KA-treated compared to control rats (Fig. 8-1C). The PS2/PS1 ratio at 50 to 100 ms interpulse intervals was *reduced* in KA-treated compared to control rats (Fig. 8-1B), suggesting an increase in paired-pulse inhibition in the DG after KA treatment. Interestingly, a small dose of $GABA_A$ receptor antagonist bicuculline, injected into the lateral ventricle, also *reduced* the PS2/PS1 ratio in control rats without inducing DG bursting (Fig. 8-1C, top trace). The same bicuculline dose given to KA-treated rats induced spike bursts in the DG, after MPP or CA3 stimulation (Fig. 8-1C). Responses in the DG of KA-treated rats suggest a compensatory increase in baseline inhibition that is susceptible to a small challenge, and we call this "fragile inhibition" (21).

Spike excitation of CA1 following low-intensity CA3 stimulation was also increased in KA-treated rats as compared to control rats (not shown). In contrast to the DG, paired-pulse spike ratio was increased in CA1 of KA-treated as compared to control rats (Fig. 8-1B). In addition, apical dendritic spike excitability was increased in KA-treated rats, as shown by the "late" spike following the second pulse in Fig. 8-1D (22). In control rats, the population spike only propagated to the proximal apical dendrites (42), similar to the early spikes (asterisks) evoked in Figure 8-1D. The late distal dendritic spike also suggested a re-excitation of CA1 after CA3 activated the EC, i.e., EC-hippocampal reverberation (21,22). The distal dendritic spikes may arise preferentially because of enhanced Na^+ and Ca^{++} channel activation (6,10) and a loss of dendritic inhibition mediated by the stratum lacunosum-moleculare interneurons (32). Direct EC excitation of CA1 was also shown to increase in the KA-treated rats, suggesting alternate, parallel routes from the EC to the hippocampus.

Behavioral Effects of Seizures

A temporal lobe seizure propagates to many parts of the brain. Convulsions indicate that secondary generalized seizures involve the motor areas. Temporal lobe seizures also spread to the thalamus, substantia nigra, and nucleus accumbens (43). Seizure-induced plasticity in these limbic or subcortical pathways causes persistent behavioral problems associated with seizures (44,45), which may be intractable to anticonvulsants.

Seizure Onset and Synchronization

How seizures start and spread is not fully understood. A local area may initiate and sustain a hippocampal AD (46,47), with the participation of recurrent excitation, inhibition, gap junction synchronization (48), and EC-hippocampal circuits (49). Recently, we found that $GABA_B$ receptors also control the threshold and onset frequency of an AD (50). In addition to the long-term changes, the onset of ADs, also depends critically on short-term plasticity. Electrical stimulation frequency in the 5- to 200-Hz range was the most effective in eliciting an AD, possibly because of both pre- and postsynaptic facilitation. Stimulation of 5 to 50 Hz tended to facilitate excitation (Fig. 8-1B), whereas high-frequency stimulation ($>$ 10 Hz) shut down $GABA_A$ receptor function (51), partly by activating $GABA_B$ autoreceptors.

In the normal state, neurons are continuously bombarded by neural and hormonal (including cytokine) signals that may decrease AD threshold. Normal brain functions, such as synaptic plasticity and arousal, also require repetitive firing of neurons and disinhibition. For example, cortical activation by cholinergic inputs is necessary for arousal and cognitive functions of the cortex, and acetylcholine mediates disinhibition of cortical neurons (52,53). One aspect of intractability is the inability of anticonvulsants to differentially suppress abnormal as compared to normal activity.

CONCLUSION: EXCITABILITY AND INTRACTABILITY

Several possible causes of intractability are revealed by physiological studies, in addition to drug transport (5). Studies in TLE models reveal persistent, seizure-induced changes in ionic channels, particularly Na^+ channels or GABA-A receptors, and these "moving targets" may affect the efficacy of an anticonvulsant drug. At the level of neural circuits, seizures may increase or decrease GABAergic function in different parts of the brain. Thus, a dose of a particular $GABA_A$ receptor agonist may suppress epileptiform activity in one structure while being toxic at another structure by causing sedation and cognitive impairment.

Neural plasticity appears to be both cause and effect of seizures. Long-term changes of GABAergic inhibition and NMDA receptor functions will make the brain more susceptible to spontaneous seizures. However, more transient and proximal events (e.g., hormonal, sensory, or behavioral changes) may activate the seizure. The physiological changes that precede a "spontaneous" seizure are not well understood. Nor is the process of epileptogenesis. However, we believe that understanding short- and long-term neural plasticity in the brain is essential for the control of intractable seizures.

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