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Journal
Epilepsy Research, 11(3)

ISSN
0896-6974

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Publication Date
1992-05-01

DOI
10.1016/0920-1211(92)90096-c

Epilepsy Res., 11 (1992) 173–182
Elsevier

EPIRES 00469

Section of the corpus callosum in kainic acid induced seizures in rats: behavioral, electroencephalographic and neuropathological study

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(Received 5 August 1991; accepted 25 January 1992)

Key words: Corpus callosum; Seizure; Status epilepticus; Kainic acid; Animal model

Clinical and experimental data suggest that the role of corpus callosum in epilepsy includes synchronization, spread, excitation and inhibition. Section of the corpus callosum (SCC) is known to be a useful therapy in selected types of generalized epilepsy, i.e., tonic, atonic and generalized convulsive seizures, but not partial seizures which may be exacerbated by this procedure. The goal of this study was to determine the effect of SCC in the kainic acid (KA) model of limbic seizures in rats. Using several doses of KA (2.5, 5 and 10 mg/kg) injected systemically, we found a potentiation of the behavioral, electrographic and histological effects of KA in the SCC group of animals compared to the sham-operated control rats. A low dose of kainic acid (2.5 and 5 mg/kg) induced status epilepticus in the SCC animals, but not in the sham-operated control rats. These data demonstrate that in the KA model of temporal lobe seizures, SCC not only fails to protect, but actually intensifies seizures. This finding is compatible with the hypothesis that there is an inhibitory influence, via the corpus callosum, of the non epileptic neocortex on its contralateral homologue in the kainic acid model.

INTRODUCTION

Kainic acid (KA) is a rigid glutamate analogue, which induces electroencephalographic (EEG) and behavioral seizures in rats[2,14]. The behavioral and EEG aspects of the seizures are dose-dependent and progress over time to status epilepticus[2,14,15]. Behavioral, EEG, metabolic, and neuropathological studies show that systemic KA preferentially activates seizures in the limbic system, particularly in the hippocampus[1,14].

The corpus callosum serves primarily to connect the neocortex[11] of the two hemispheres, while the ventral hippocampal commissure connects the hippocampus of each side[25]. Experimentally, the role of the corpus callosum in epilepsy has been documented in a number of animal models of generalized or focal seizures in the cat, monkey and rat[3]. Erickson[8] showed that the corpus callosum is a substrate for propagation, bilateralization and generalization of partial seizures. The corpus callosum has also been found to be necessary for bilateral synchronization of epileptic discharges in the feline generalized penicillin epilepsy model[20],

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pentylenetetrazol induced seizures in rats[18] and in the genetic model of absence in rats[32].

In addition to mediating spread and synchronization of epileptiform discharges, interhemispheric connections may have either inhibitory or excitatory function. Wada et al.[19,33] showed an inhibitory role of interhemispheric connections in the amygdala kindling model in the rat and cat. However, complete section of the corpus callosum prevents the development of status epilepticus in the lithium-pilocarpine model of status epilepticus in rats[27], suggesting an excitatory role of interhemispheric connections via the corpus callosum in this model.

In the human, the available literature suggests that section of the corpus callosum (SCC) has a therapeutic benefit in selected types of generalized seizures that include tonic, atonic and tonic-clonic seizures[3,30]. Spencer et al.[28] reported that focal seizures were more intense after corpus callosum section. They argued for an inhibitory influence of the contralateral hemisphere.

However, there are few experimental data that address the efficacy of SCC in experimental models of seizures.

The goal of this study was to determine the effect of corpus callosum sectioning in the kainic acid model of focal limbic seizures and status epilepticus in rats.

MATERIAL AND METHODS

Sprague-Dawley rats (n = 45) (Harlan Co. Indianapolis) weighing 200–280 g at the time of surgery were used for all experiments. Animals were maintained on a 12-h day/night cycle and allowed free access to food and water.

SCC (n = 15) was performed stereotactically under halothane anesthesia as previously described[32]. During the same surgical procedure, four cortical stainless steel electrodes were implanted. Depth recordings were obtained from bipolar twisted concentric enameled stainless steel electrodes (tip diameter 100 μm, vertical interelectrode distance 1 mm) placed in the dorsal hippocampus (anteroposterior (AP) −4 mm, mediolateral (ML) 2 mm, dorsoventral (DV) 4 mm, reference from bregma)[24].

There were two surgical control groups: (1) a sham-operated group of animals (n = 15) had section of the skull and the longitudinal sinus, and electrode implantation; (2) the second control group (n = 15) had an electrolytic lesion (2 mA, 20 s) of the ventral hippocampal commissure (AP −1.3 mm, DV 5 mm, ML 0 mm) and electrode implantation, but no callosal section and limited damage to the midline sinus. This control group was necessary because complete SCC almost always damaged the ventral hippocampal commissure as well.

Surgery was well tolerated with no deaths.

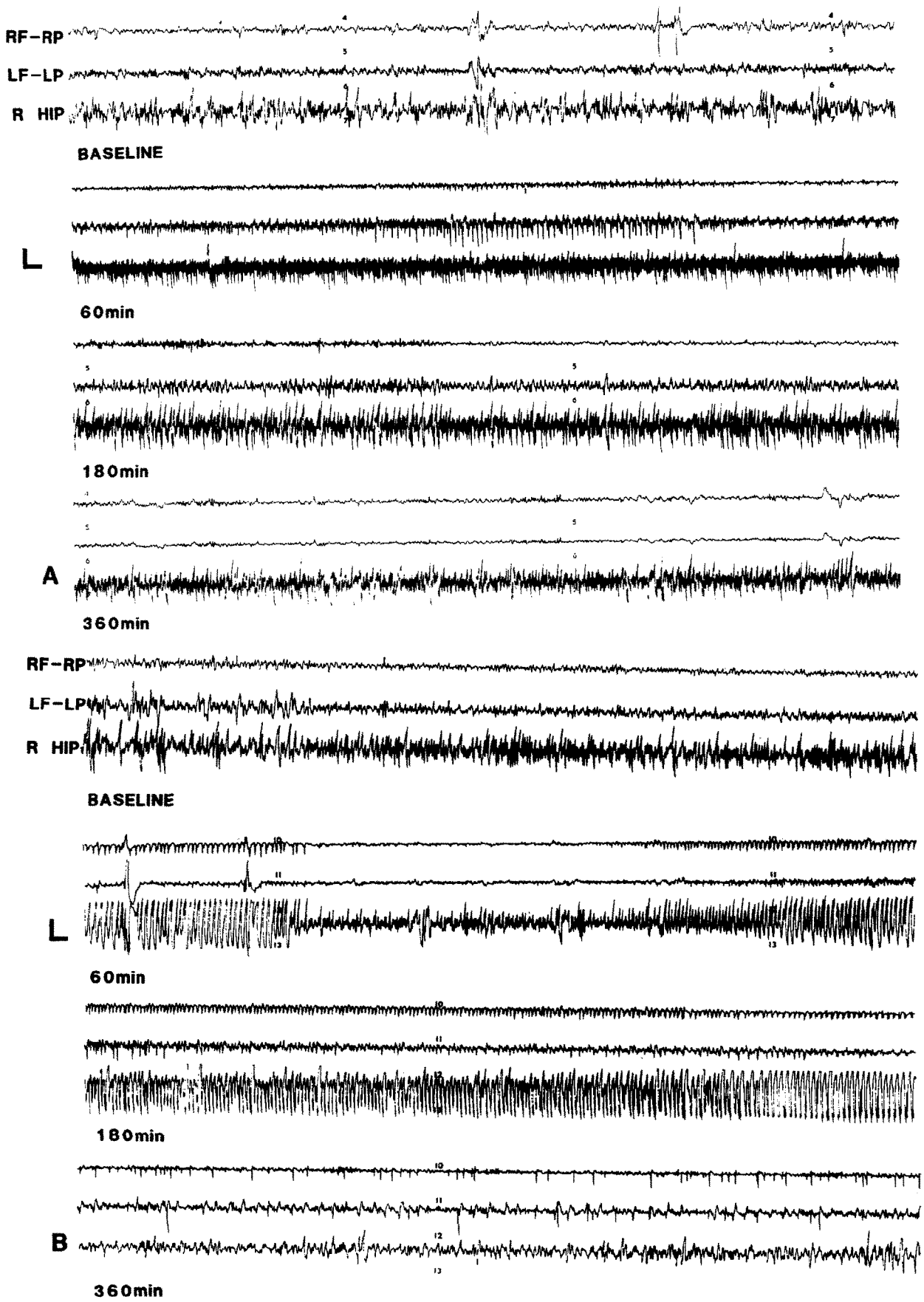
After 5–6 days of recovery, EEG was recorded from freely moving animals with a 16-channel Grass polygraph 30 min prior to subcutaneous injection of kainic acid (Sigma, St. Louis) dissolved in saline. Three doses of kainic acid were utilized: 2.5 mg/kg, 5 mg/kg, 10 mg/kg. EEG and behavior was observed continuously for 5–6 h after kainic acid injection.

Kainic acid caused several clearcut behavioral alterations which could be divided into three stages[15].

Stage 1 was defined as staring.

Stage 2 consisted of automatisms and mild limbic convulsions. This included head bobbing, sniffing, blinking, chewing, yawning and twitching of the

Fig. 1. (A) Electrographic activity recorded from a sham-operated rat following systemic administration of KA 2.5 mg/kg. 60 min after KA injection, hippocampal theta rhythm is replaced by fast activity (25–30 Hz) while a single electrographic seizure is recorded in the left cortical leads. 180 min after KA injection cortical discharges have returned to baseline. (B) Electrographic activity recorded from an SCC rat following systemic administration of KA 2.5 mg/kg. 60 min after KA injection, hippocampal theta rhythm is replaced by fast activity and repetitive sharp waves while frequent unilateral right seizures are recorded in the cortex. 180 min after KA injection, continuous spikes and sharp waves are present in cortical and hippocampus leads. 360 min after KA injection, bilateral asynchronous spikes are seen in cortical leads. R, right; L, left; F, frontal cortex; P, parietal cortex; HIP, hippocampus. Scale: horizontal 1 s, vertical 100 μV.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vibrissae.

Stage 3 was severe limbic convulsions, including salivation, rearing, forelimb clonus and falling.

The corticographic seizures were characterized by unilateral or bilateral synchronous spikes and sharp waves. Status epilepticus was defined as continuous unilateral or bilateral spikes and sharp waves.

The mortality at 24 h was noted and the survivors were killed by decapitation at 72 h. Coronal frozen sections (25 μm) were stained with cresyl violet and examined microscopically to ascertain the extent of SCC and the presence of brain lesions related to the seizures.

RESULTS

Behavior

In the sham-operated control group, kainic acid induced behavioral alterations in a dose-dependent fashion. Increasing doses resulted in staring (2.5 mg/kg) stage 1, sniffing, head bobbing (5 mg/kg) stage 2, which progressed at a dose of 10 mg/kg to salivation, occasional rearing, forelimb clonus, and falling stage 3.

In the group with lesion of the ventral hippocampal commissure, kainic acid induced the same behavioral alterations as in the sham-operated control group.

In the SCC group KA 2.5 mg/kg (n = 5) induced stage 2 seizures in four animals. KA 5 mg/kg induced a stage 3 seizures in all animals tested. With 10 mg/kg of kainic acid severe limbic convulsions were more frequent and sustained compared to either sham-operated or ventral hippocampal lesioned controls.

None of the control animals died within the first 24 h. One animal in the SCC group died within the first 24 h after injection of KA 5 mg/kg.

EEG findings

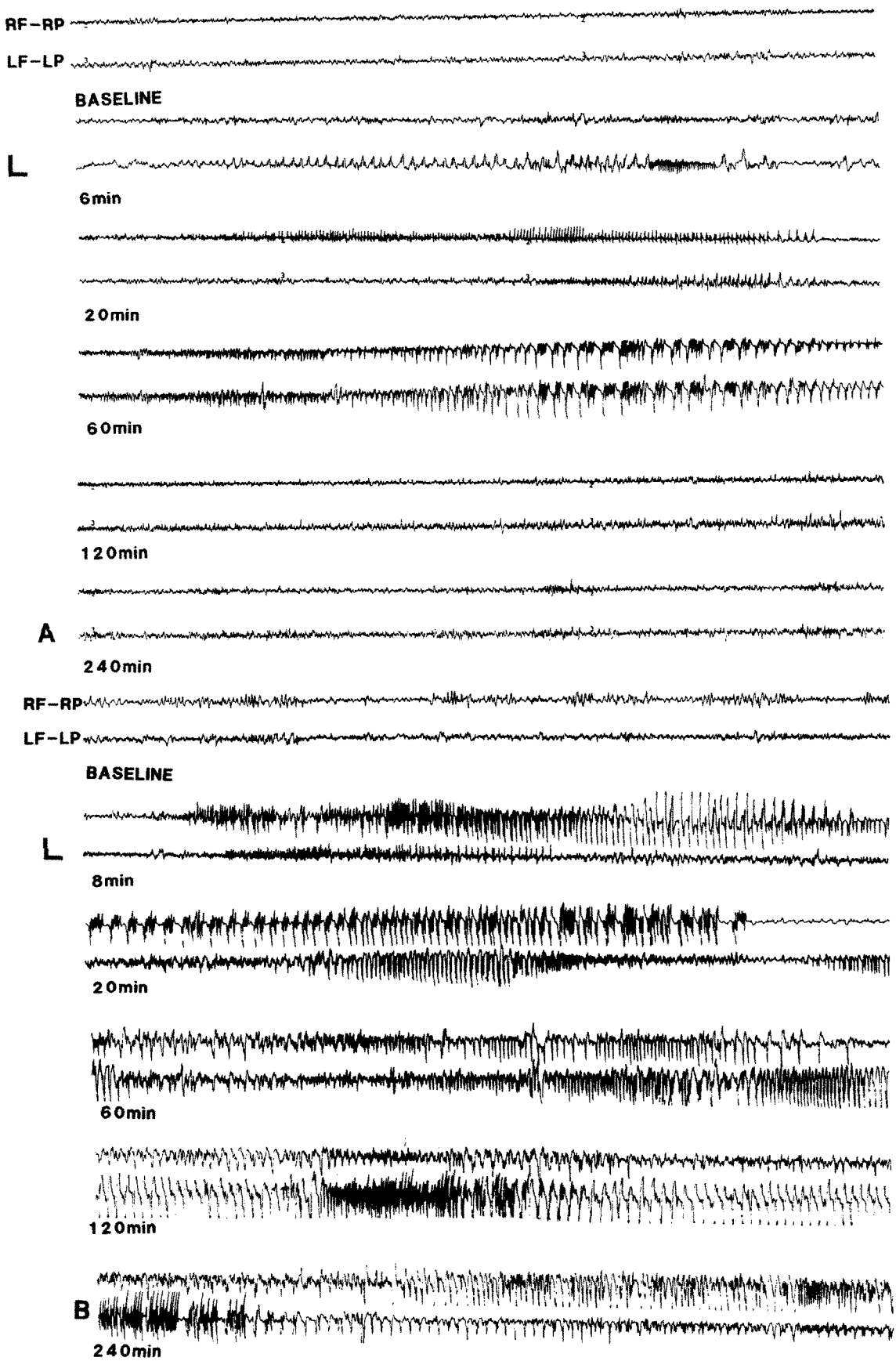
Sham-operated control group. KA 2.5 mg/kg (n = 5): The normal hippocampal theta rhythm was initially replaced by fast activity (25–30 Hz) in all animals (Fig. 1A). Three animals exhibited unilateral or bilateral electrographic seizures accompanied by a behavioral stage 1 seizure. None of the animals exhibited status epilepticus. The mean latency to the last cortical seizure was 167 ± 43 min; subsequently the cortical EEG returned to baseline in all animals.

KA 5 mg/kg (n = 5) (Fig. 2A) was associated with unilateral left or right cortical seizures of 20–60 s duration accompanied by behavioral stage 1 seizures in all animals. This was followed by bilateral synchronous cortical seizures with a maximum frequency of one every 2 min and accompanied by a behavioral stage 2 seizure. None of the animals exhibited status epilepticus at this dose of KA. The mean latency to the last cortical seizure was 146.9 ± 27.3 min and the cortical EEG returned to baseline at the end of the last seizures in all animals.

KA 10 mg/kg (n = 5) (Fig. 3A) induced unilateral electrographic seizures accompanied by a behavioral stage 1 seizure, followed by bilateral synchronous and asynchronous electrographic seizures accompanied by a behavioral stage 2 seizures which then evolved into a poorly synchronized status epilepticus associated with a behavioral stage 3 seizure in all animals tested. Bilateral continuous sharp wave persisted for at least 6 h after kainic acid injection at this dose (see also Table I).

Ventral hippocampal commissure lesioned group. Kainic acid 2.5 mg/kg (n = 5) induced unilateral and bilateral electrographic seizures accompanied by a behavioral stage 1 seizure in four animals.

Fig. 2. (A) Electrographic activity recorded from a sham-operated rat following systemic administration of KA 5 mg/kg. 6 min after KA injection a left cortical seizure is recorded, followed 14 min later by an initially unilateral and secondarily bilateral cortical seizure. 60 min after KA injection a bilateral synchronous seizure is recorded. 120 min after KA injection cortical discharges have normalized. (B) Electrographic activity recorded from an SCC rat following systemic administration of KA, 5 mg/kg. 8 min after KA injection a bilateral asynchronous seizure is recorded followed 52 min later by bilateral asynchronous status epilepticus which persisted for 3 h. R, right; L, left; F, frontal; P, parietal. Scale: horizontal 1 s, vertical 100 μV.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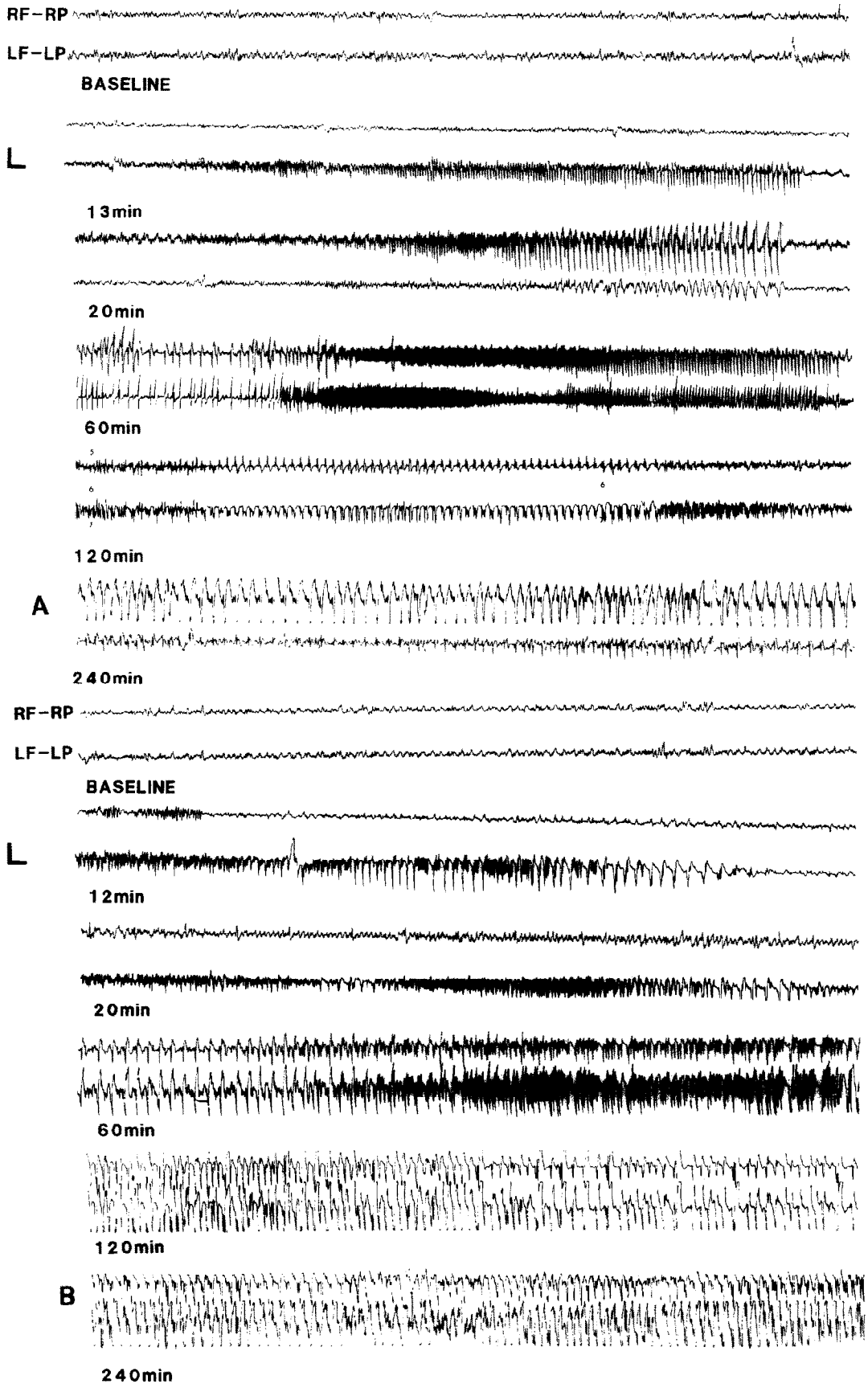
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TABLE I

Latency to first seizure and status epilepticus (S.E.)

Kainic acid (mg/kg)	*Sham-operated*		*VHC lesioned*		*SCC*	
	latency (min) to first seizure	*latency (min) to S.E.*	*latency (min) to first seizure*	*latency (min) to S.E.*	*latency (min) to first seizure*	*latency (min) to S.E.*
2.5	17.5 ± 1.6 (n = 3)	not seen	40.7 ± 14.8 (n = 4)	not seen	35.7 ± 5.3 (n = 5)	57.2 ± 7.3 (n = 5)
5	17.3 ± 5.1 (n = 5)	not seen	25.2 ± 5.7 (n = 5)	not seen	18.0 ± 3.6 (n = 5)	86.2 ± 24.4 (n = 5)
10	11.6 ± 4.2 (n = 5)	72.0 ± 9.3 (n = 5)	6.4 ± 1.2 (n = 5)	51.6 ± 3.4 (n = 5)	12.0 ± 2.8 (n = 5)	42.8 ± 6.5 (n = 5)

VHC, ventral hippocampal commissure. Results are expressed as means ± SE.

None of the animals exhibited status epilepticus. The mean latency to the last cortical seizure was 96.6 ± 37.0 min; subsequently the cortical EEG returned to baseline.

KA 5 mg/kg (n = 5) induced unilateral and bilateral cortical seizures accompanied by a behavioral stage 2 seizure in all animals. One animal exhibited status epilepticus with a latency of 59 min but did not progress beyond a behavioral stage 2 seizure. In the other four animals, the mean latency to the last cortical seizure was 133.0 ± 15.5 min. The EEG returned to baseline at the end of the last seizure in all but one animal.

KA 10 mg/kg (n = 5) induced seizures accompanied by a behavioral stage 2 seizure which progressed to status epilepticus in all animals. Bilateral continuous sharp wave persisted for at least 6 h after kainic acid injection.

SCC group. KA 2.5 mg/kg (n = 5) induced fast activity (25–30 Hz) in the hippocampus and unilateral and bilateral synchronous seizures with high frequency (at least one per minute) in all animals (Fig. 1B). Four animals exhibited status epilepticus accompanied by behavioral stage 2 seizures. After 6 h the EEG was still abnormal, showing bilateral asynchronous spikes.

KA 5 mg/kg (n = 5) induced unilateral and bilateral asynchronous seizures after a mean latency of 18.0 ± 3.6 min (Fig. 2B). All animals developed poorly synchronized electrocorticographic EEG status epilepticus accompanied by behavioral stage 3 seizure, with a mean latency of 86.2 ± 24.4 min. Status epilepticus persisted for at least 6 h after KA injection.

KA 10 mg/kg (n = 5) induced unilateral and bilateral seizures in all animals (Fig. 3B). Poorly synchronized electrographic status epilepticus, accompanied by behavioral stage 3 seizure and sustained forelimb clonus, developed in all animals. Status epilepticus persisted for at least 6 h after KA injection.

Neuropathological effects of KA

Forty-five animals were examined. In the sham-operated control group (n = 15), neuropathological changes correlated with the dose of KA. An asymmetric, focal loss of neurons in CA3 of the hippocampus was seen in all five animals at the dose of 2.5 mg/kg. 5 mg/kg (n = 5) induced similar

Fig. 3. (A) Electrographic activity recorded from a sham-operated rat following systemic administration of KA 10 mg/kg. 13 min after KA injection a left cortical seizure is recorded followed 7 min later by a bilateral seizure and 47 min later by a bilateral poorly synchronized status epilepticus which persisted for at least 3 h. (B) Electrographic activity recorded from an SCC rat following systemic administration of KA 10 mg/kg. 12 min after KA injection a left cortical seizure is recorded followed 48 min later by bilateral status epilepticus persisting for at least 3 h. R, right; L, left; F, frontal; P, parietal. Scale: horizontal 1 s, vertical 100 μV.

but bilateral lesions, which were more severe with the 10 mg/kg dose (n = 5). In addition four animals showed large asymmetric regions of necrosis in several brain regions, including piriform cortex, lateral olfactory tubercle, endopiriform nucleus and anterior amygdaloid area.

In the ventral hippocampal commissure lesioned group, 3/15 animals had an associated mild lesion of the triangular septal nucleus and the dorsal fornix. Kainic acid 2.5 mg/kg, 5 mg/kg and 10 mg/kg (n = 15) induced the same neuropathological changes observed in the sham-operated control group, except that the additional lesions in the ventral forebrain area were seen in only two animals.

In the SCC group (n = 15), the SCC was found to be complete in 14 animals and limited to the posterior two-thirds in one. The ventral hippocampal commissure was sectioned in 13 animals. Neuropathological changes were related to the dose of KA. Lesions were similar but more severe than those of the control groups at all KA doses. However, no ventral forebrain lesions were found.

DISCUSSION

These data demonstrate no protective effect of complete SCC against seizures and status epilepticus in the kainic acid model. Rather, SCC potentiates KA induced seizures and the resulting brain lesions. This effect of SCC is independent of skull, longitudinal sinus, and ventral hippocampal commissure lesions.

The behavioral, EEG, and neuropathological changes in our sham-operated control group were similar to those previously described in kainic acid induced seizures and status epilepticus[2,14,15,26].

The mechanisms underlying the potentiation of KA induced seizures by SCC are unclear. The corpus callosum, ventral hippocampal commissure and anterior commissure may participate at different levels in the bilateral synchronization of epileptic discharges and spread, depending on the type and site of origin of the seizures[16–21]. Previous studies along with the current data show that the EEG seizures induced by KA are poorly synchronized (Figs. 1A, 2A, 3A). SCC (Figs. 1B, 2B, 3B) or lesion of the ventral hippocampal commissure did not significantly alter electrocorticographic seizure synchronization. This is in agreement with Collins et al.[7], who showed a weak role of the commissural system in the functional anatomy of limbic seizures.

The available literature on the functional role of the hippocampal commissure in temporal lobe seizure in human is controversial. Lieb and Babb[13] reported that commissural connections between the hippocampal formation are unimportant, while Spencer et al.[29] suggested the existence of an operational hippocampal commissure. In the amygdala kindling model in cats, the hippocampal commissure is involved in mediation of the transhemispheric positive transfer effect[9]. The current study however suggests that in the kainic acid model of temporal lobe epilepsy, the ventral hippocampal commissure plays a weak role, since animals with lesion of the ventral commissure alone developed a similar behavioral, EEG and neuropathology to the sham-operated control group.

We have previously demonstrated the protective effect of complete SCC against status epilepticus and death in the lithium-pilocarpine model[27]. However, the kainic acid and lithium-pilocarpine models differ on several points. Lithium-pilocarpine seizure activity is first detected in the ventral forebrain and secondarily spreads to the neocortex[4], whereas seizures induced by kainic acid appear to originate in the hippocampus[2,14,15]. Kainic acid seizures entail a gradual buildup with unilateral asynchronous EEG seizures and progressive spread of electrographic activity through the limbic system while lithium-pilocarpine induced seizures typically become generalized much more rapidly. Lithium-pilocarpine induces symmetric necrosis in the ventrolateral forebrain[4,27,31] while kainic acid induces loss of neurons in the hippocampus[14,26]. Using 2-deoxyglucose quantitative autoradiography Clifford et al.[4] reported a higher rate of glucose consumption in the corpus callosum and an increased glucose utilization in the ventral pallidum, the substantia nigra, the neocortex and the entire limbic system in the lithium-pilocarpine model. In kainic acid induced seizures, Collins et al.[6] reported an increase in glucose utilization in the entire limbic system during stage 3 seizure, while the glucose utilization in the neocortex was

depressed. Those authors postulated an inhibition of the neocortex during the stage 3 seizure[6].

A hypothetical basis for the potentiation by SCC of KA induced seizures is that the neocortex and the hippocampus of each hemisphere exert an inhibitory influence via the corpus callosum on the development of epileptogenic processes on its contralateral homologue. Douglas et al.[5] showed that stimulation of the contralateral hippocampus had a marked inhibitory effect on granule cell excitability in the dentate fascia in rats. Mutani et al.[21,22], studying the mechanisms of interaction of asymmetrical bilateral epileptogenic foci in cat neocortex, suggested that callosal connections mediated an interhemispheric inhibitory influence. Ottino et al.[23], studying the mechanisms of interaction of symmetrical bilateral epileptogenic foci in cat neocortex, demonstrated that splitting of the corpus callosum and hippocampal commissure disrupted bilateral synchrony of epileptic discharges without affecting the frequency of the discharges. These data are compatible with the hypothesis that in the current experiments SCC suppressed the inhibitory influence of the non epileptic neocortex and hippocampus on its contralateral homologue in the kainic acid model.

Our results are consistent with the results of a clinical study in which more intense focal seizures occurred after SCC[28]. The current study also validates the use of the kainic acid model as an animal model of temporal lobe seizures since this form of seizure is not helped, and may be made worse by corpus callosotomy[3,30].

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