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Effects of Corpus Callosum Stimulation on the Morphology and Frequency of Epileptic Bursts in the Feline Topical Penicillin Generalized Model

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Abstract. Twelve cats were stimulated at the rostrum of the corpus callosum while full epileptic activity was recorded after topical application of penicillin on the cortex bilaterally. Electrocorticography was performed bilaterally. In 6 animals the electrode position was checked by evoked potentials. Stimulation parameters ranged from 0.5 to 1,000 Hz, from 2 to 10 mA, and from 0.5 to 5.0 ms. No significant modification was found in frequency, synchrony, and morphology of the epileptic bursts and spikes, suggesting that callosal stimulation, at least using this model, is ineffective in reducing epileptic activity.

Introduction

Corpus callosum section has been used as a palliative surgery for control of otherwise medically intractable multiform seizures in multifocal and/or frontal epilepsies with secondary generalization [2, 6, 9, 18, 20]. Experimental, clinical, and surgical studies have reinforced the role of corpus callosum as the major pathway for the secondary generalization of seizures [7, 10–13, 16]. Although callosotomy seems to be a very safe procedure, disconnection syndromes frequently occur in one-step total callosotomy [4] and a discrete neuropsychological syndrome has also been described following selective anterior callosotomy [3].

Callosotomy can stop the spread of epileptiform discharges from one hemisphere to the other, but Mutani and Durelli [12] showed in cats that the activity of individual foci is not reduced by this procedure and could even become more intense. This is in agreement with the

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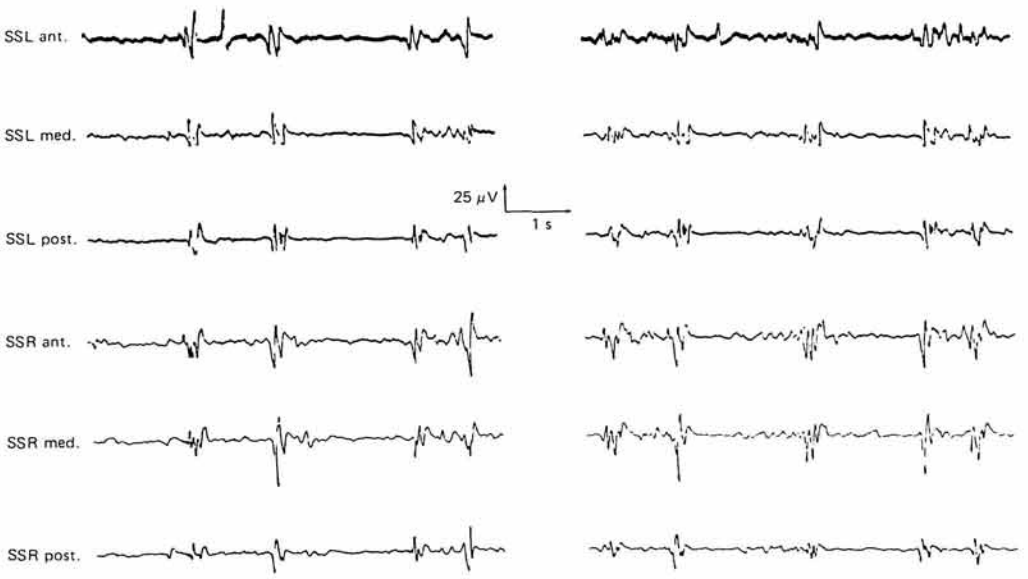

Fig. 1. Pre- and poststimulus epileptic activity recordings. SSL = Left suprasylvian gyrus; SSR = right suprasylvian gyrus; ant. = anterior; med. = media; post. = posterior.

finding that some callosotomy patients go into partial status epilepticus [Marino Jr., unpublished observation] or have their partial seizure frequency increased weeks after surgery [17].

In the present study, callosal stimulation experiments were performed in an attempt to achieve a functional (reversible) section of the corpus callosum and to analyze the effects of callosal stimulation on morphology, synchrony, and frequency of the epileptic bursts.

Methods

Twelve adult cats were anesthetized with intramuscular ketamine, 30 mg/kg. Brachial veins were dissected for infusion of drugs as necessary. The trachea was intubated with a human infant cannula, and the animal was attached to a stereotactic frame, paralyzed with intravenous gallamine, and artificially ventilated with a Takaoka respirator.

An extensive bilateral craniotomy was performed leaving only a narrow strip of bone over the sagittal sinus with a wide exposure of the marginal, suprasylvian, and syl-

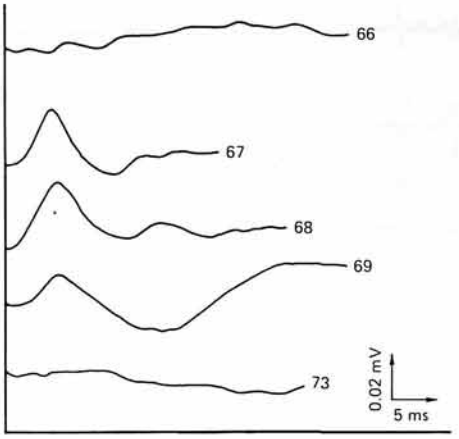

Fig. 2. Callosal localization through evoked potentials. Lesion at the stereotactic coordinate 68 proved to be exactly in the middle of the corpus callosum. The characteristic morphology of callosal-mediated evoked potentials appears close to that point and is lost away from it.

vian gyri after the opening of the dura. Two pieces of filter paper which exactly fit the exposed cortical surfaces were placed over them. Silver electrodes (2 to 8) were placed over the filter papers, and electrocorticography (ECoG) was performed using a Beckman polygraph. The more anterior ECoG electrode was always placed at the points where callosal fibers from the stimulation site were expected to end (see below). Stainless steel unipolar or bipolar electrodes were aimed at the rostrum of the corpus callosum following stereotactic coordinates. In 5 animals the position of the electrodes at the corpus callosum was checked by stimulating that point and recording from the cortical points where callosal fibers were expected to end. This turned out to be a very accurate way of guiding the electrode, since even a 0.5-mm deviation of the electrode completely modified the morphology of the cortical surface evoked potentials (fig. 1).

Penicillin (200 IU) was then applied to each hemisphere by dropping 0.4 ml of saline with penicillin over the filter papers. Both video and slow-paper speed ECoG continuous recording monitored the appearence of the epileptic bursts which occurred 10–35 min after the initial instillation. Basal epileptic ECoGs were obtained and then callosal stimulation was started: square pulses with a duration of 0.5–5 ms, a frequency of 0.5–1,000 Hz, and a current of 2–10 mA were applied.

Intrastimulation ECoGs were obtained when the frequency was less than 5 Hz. For all stimulatory parameters pre- and poststimulus recordings were obtained. Morphology, synchrony, and frequency of the epileptic bursts were then analyzed. Animals were finally sacrificed, and the electrode positions were checked histologically on Nissl-stained sagittal and coronal sections of the brain.

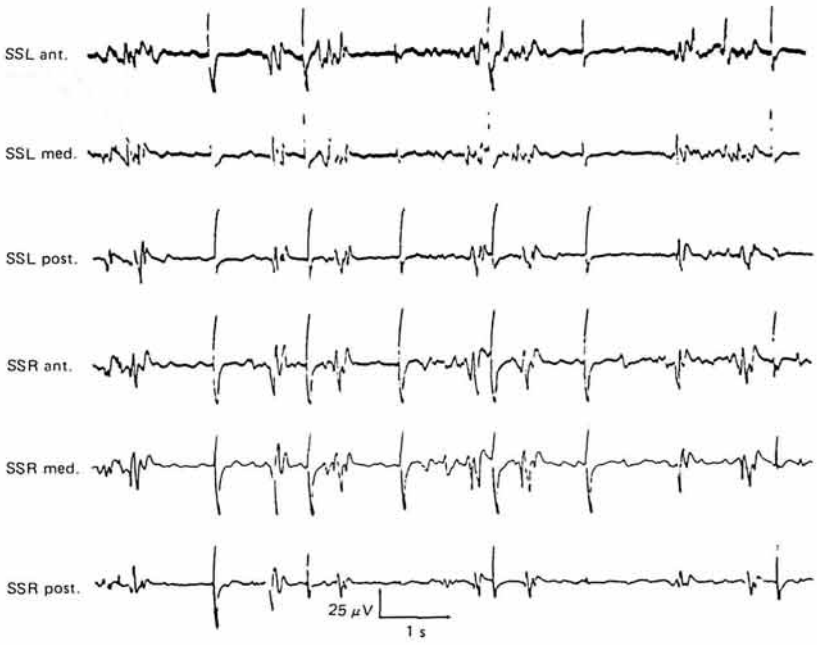

Fig. 3. Intrastimulation recording showing stimulus artifacts randomly in relation to bursts. No modification of the ongoing burst was induced by stimulation. For explanation of abbreviations see figure 1 legend.

Results

Epileptic burst morphology and frequency were very similar to those described by Gloor et al. [5]. No significant change in morphology or frequency after callosal stimulation was found in the epileptic bursts, even by increasing frequency, duration, and current. A sample of pre- and poststimulus ECoGs is shown in figure 2.

With stimulation frequencies less then 5 Hz, intrastimulation analysis was feasible. Callosal stimulation artifacts could be seen randomly in relation to the epileptic bursts. Even when a stimulus met an ongoing burst, no modification of its morphology or course could be noted (fig. 3).

In some instances, a small part of the cingulate gyrus was simul-

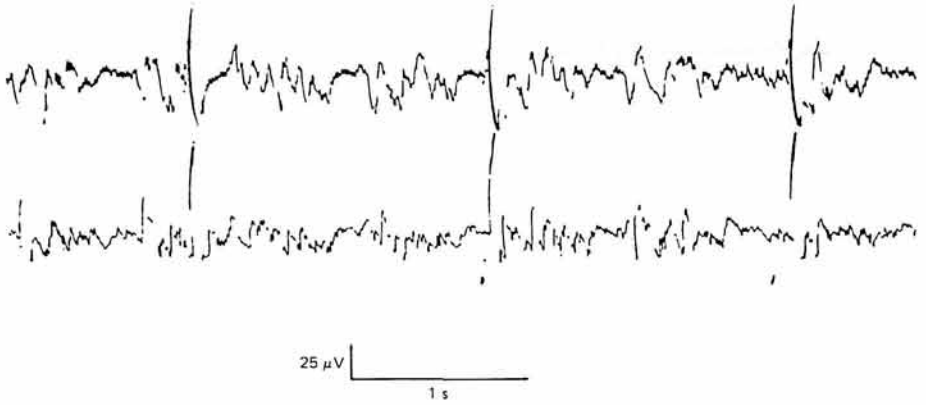

Fig. 4. Cingulate-driven bursts. Upper trace: left hemisphere; lower trace: right hemisphere.

taneously stimulated (confirmed histologically), and in such cases numerous cingulate-driven bursts were recorded (fig. 4).

Inserting the electrodes slightly deeper resulted in isolated callosal stimulation and disappearance of the driven bursts. Epileptic bursts persisted strictly synchronous in most cases during the course of stimulation, showing that a functional inactivation of the corpus callosum was not being achieved.

Discussion

When introducing the model of feline topical penicillin generalized epilepsy, Quesnay et al. [15] had already studied the effect of stimulating some structures on the appearance of recruiting responses. The corpus callosum was found to be a region with a poor recruiting response when compared to thalamic and cingulate regions. This is in agreement with our findings that driven bursts only appeared when the cingulate gyrus was also stimulated, directly or indirectly. In fact, we were looking for the opposite effect, i.e., the ability of corpus callosum

to inhibit the bursts. Callosal section may increase individual foci activity which could mean that the overall callosal activity (which certainly might include inhibitory and facilitatory fibers) is inhibitory, at least in this preparation, so that callosal stimulation might decrease the epileptic activity.

Our findings are not in agreement with this. It has to be pointed out that at least two (one on each hemisphere) electrodes of the ECoG recordings must be positioned at the points where callosal evoked potentials had demonstrated the termination of the stimulated fibers of the corpus callosum, since local effects could be triggered by stimulation of the corpus callosum. Nevertheless, no modification in any cortical region activity occurred with callosal stimulation.

Kostopoulos et al. [8] showed that the bursts in the present model derive from modifications of the sleep spindles, and other authors [1–14] have shown that they are highly dependent upon thalamic inputs, although similar activity has been found in isolated cortex experiments. This might not be the case in multifocal epilepsies. Callosal stimulation using a focal epilepsy model is currently being carried out in our laboratory. Wise and Jones [19] showed that at least in rat somatic sensory cortex callosal and thalamic afferents to the cortex do not share the same topographic distribution. This might play a role in the inefficiency of callosal stimulation to reduce epileptic burst activity in an epilepsy model highly dependent on the thalamus.

Corpus callosum evoked potential mapping has shown that focal callosal stimulation acts upon a reduced cortical region, that callosal evoked potentials could be used to check the electrode sites in experimental animals and that it could be used in human procedures.

In summary, callosal stimulation (at least using the present model) was ineffective in altering epileptic burst activity in terms of morphology, synchrony, and frequency. Nevertheless, callosal functional sectioning by stimulation for treatment of multifocal and/or frontal epilepsies should be further evaluated.

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