WHY ARE COMPLEX PARTIAL SEIZURES INTRACTABLE?

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Dr. Burnham argues that data from animal studies—and especially kindling studies—can provide insights into why complex seizures are so common and drug resistant.

INTRODUCTION

Complex partial seizures are the most common seizures in adults, and some of the most drug resistant. They most commonly arise in the temporal lobes, and involve the limbic structures.

Why do the limbic structures so often give rise to epileptic discharge, and why does that discharge resist drug control? Animal studies—and particularly studies involving the kindling model—provide some insights into this question.

THE KINDLING MODEL

The kindling model is an animal model of partial epilepsy in which stimulating electrodes are implanted chronically into the forebrain—often into a limbic structure—and low-intensity current is used to trigger focal seizure activity. With repetition, the focal seizures begin to propagate into more and more extra-focal sites, until eventually secondarily generalized motor seizures occur. Thus, limbic kindling provides a model of partial limbic seizures, secondarily generalized.
SEIZURE THRESHOLDS IN LIMBIC STRUCTURES: KINDLING STUDIES

An important feature of the kindling model—which distinguishes it from other partial seizure models—is that seizure thresholds can easily be measured through the chronically implanted electrodes. This has been done in a large number of studies, providing a sizable amount of information on seizure thresholds in different parts of the brain. Table 1 summarizes the data from studies in which thresholds for electrical stimulation were measured in male, Long-Evans rats using the following standard kindling parameters: one second of 60 Hz, balanced biphasic (positive- and negative-going) 1 ms square-wave pulses. All values are peak-to-peak.

As Table 1 indicates, thresholds are different in different parts of the brain. The lowest thresholds are seen in the limbic structures. The threshold in the amygdala, for instance, is often around 100 $\mu$A. The hippocampal threshold is also around 100 $\mu$A and may actually be lower, especially in the dorsal hippocampus. Curiously, septal thresholds are higher, being around 300–350 $\mu$A. Still, limbic thresholds are generally low, and the amygdaloid and hippocampal thresholds are some of the lowest in the brain.

Thresholds in juxtallo (limbic) cortex (4–5 layered) tend to be somewhat higher. The threshold in the piriform cortex—closely associated to the amygdala—is around 130 $\mu$A, whereas the threshold in the cingulate is 175–200 $\mu$A. Data on the other limbic cortices are lacking, but the impression is that thresholds in limbic cortex are higher than thresholds in the amygdala or hippocampus.

Thresholds in the neocortex are distinctly higher, often around 300 $\mu$A, and the threshold in the brain-stem reticular core is extremely high. In the brain-stem reticular core—with 10 seconds of stimulation—threshold is 700 $\mu$A to 1,000 $\mu$A.

Thus, the amygdala and hippocampus have the lowest thresholds in the brain for electrical seizures, whereas the brain stem has some of the highest. Assuming that these data can be generalized to spontaneous seizures in humans, they would explain why seizures seldom arise in the brain stem whereas the amygdala and hippocampus frequently initiate seizures and are often targets for seizure surgery.

THRESHOLD DROP IN LIMBIC STRUCTURES: KINDLING STUDIES

Thresholds are not only low in limbic structures, they tend to drop lower with repeated activation.

Data in this field must be viewed with some caution, since Loscher et al. have recently demonstrated a spontaneous drop in amygdaloid threshold during the first month after electrode implantation. This spontaneous drop—which is unrelated to stimulation—disappears by two months.

Data from studies in which stimulated threshold drop was measured two or more months after implantation are summarized in the second column of Table 1. The data are limited, but they seem to indicate that the largest drops occur in the amygdala (60%), with moderate reductions being seen in the pyriform and cingulate cortex (40%). Smaller reductions occur in the neocortex and brain-stem reticular formation (20–30%). Curiously, thresholds in the hippocampus show only a very small reduction (around 25%). This may relate to the fact that they are so low to begin with.