

ANTIEPILEPTOGENESIS BY DEEP BRAIN STIMULATION

Low-frequency Stimulation of the Kindling Focus Delays Basolateral Amygdala Kindling in Immature Rats

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Stimulation of deep brain sites is a new approach for treatment of intractable seizures. In adult rats, low-frequency stimulation (LFS; 1–3 Hz) of the kindling site interferes with the course of kindling epileptogenesis. In this study we determined whether the LFS is effective against the fast kindling in the basolateral amygdala in immature, 15-day-old rats. LFS (15 min of 1-Hz stimulation) was applied after each of the 1-s, 60-Hz kindling stimulus. LFS suppressed afterdischarge duration and seizure stage throughout the course of kindling, which indicates a strong antiepileptogenic potential. As the kindling and LFS stimulation patterns are similar to those used for induction of long-term potentiation and long-term depression (LTD), respectively, LTD or depotentiation may play a role in the mechanism of action.

COMMENTARY

The potential of brain stimulation for the treatment of medically refractory epilepsy has intrigued neurologists and neurosurgeons for decades. In the early 1970s, Cooper reported that prolonged stimulation of the cerebellar cortex and anterior thalamic nuclei reduced the frequency and severity of generalized and partial seizures, but the limited controlled trials carried out in subsequent years attempting to confirm these observations were not encouraging (1). More recently, case reports have suggested that high-frequency stimulation of the subthalamic nucleus may be useful in epilepsy therapy (2). The physiologic mechanisms through which seizures may be controlled by deep-brain stimulation are poorly defined. It is often said that the stimulation in some way “jams” the circuits responsible for seizure generation, but the circuits involved and even whether the stimulation excites or inhibits neurons

are not known. Recent studies on synaptic plasticity (activity-dependent modifiability in the strength of synaptic transmission) have provided a scientific basis for the proposition that electrical stimulation not only could protect against seizures, but when appropriately applied also may reverse epileptogenic processes.

Brief high-frequency activation (typically 60 Hz for 1 s) of excitatory synapses in the hippocampus, neocortex, amygdala, and other brain regions often leads to an enduring enhancement of the strength of synaptic transmission in the activated synapses, a form of synaptic plasticity called long-term potentiation (LTP) (3). Repeated application of this type of stimulation in experimental animals, particularly in the amygdala, may lead to the development of focal epilepsy. Such kindling stimulation initially is behaviorally innocuous, but over time, elicits increasingly more robust limbic seizures. (Amygdala-kindling stimulation is often imposed daily in adult animals but can be delivered as frequently as every 30 min in immature animals, which kindle faster.) Although there are obvious similarities between LTP and kindling, the cellular underpinnings differ in many respects. Nevertheless, lessons learned from studies on LTP may suggest ways in which brain stimulation can interfere with or reverse kindling.

In the hippocampus, prolonged LFS (typically 1 Hz for 10–15 min) may elicit long-term depression (LTD), a process that is functionally opposite to LTP in that there is an enduring reduction in the efficacy of synaptic transmission. LFS also can “depotentiate” synapses that have previously undergone LTP. Given the parallels between LTP and kindling, could LFS produce a reversal of kindling? The amygdala—particularly the basolateral nucleus—is the most common site for kindling in experimental animals. In the basolateral amygdala (in contrast to the situation in the hippocampus), LFS can produce an LTP-like enhancement of synaptic strength (4). However, when LFS is imposed 10 min after a 1-s high-frequency tetanus, persistent LTD occurs (5). This phenomenon—observed in *in vitro* electrophysiological recordings in brain slices—represents an example of “metaplasticity” in which the history of synaptic experience alters the direction of synaptic plasticity.

Now Velíšek et al. have found that basolateral amygdala kindling in immature rats can be dramatically retarded when 15 min of LFS is imposed 10 min after the high-frequency

kindling stimulation in a paradigm that closely matches that used to produce LTD in the amygdala brain-slice experiments (5). One might naively assume that if a little stimulation induces kindling, then more stimulation might promote kindling. Contrary to intuition, however, Velišek et al. report that the additional LFS can decisively interfere with the development of behavioral kindled seizures and their electrical accompaniment, the afterdischarge. This observation raises the possibility that local electrical stimulation in a situation predisposing to the development of epilepsy (for example, after a brain insult) could prevent the evolution of epileptogenic processes. Moreover, it also is conceivable that appropriately patterned brain stimulation could “depotentiate” an epileptic focus in a situation in which epilepsy is already established. Of course, it has yet to be demonstrated that kindling is a relevant model for human epilepsy, and, even if this were the case, it is not apparent how curative brain stimulation would in practice be delivered so that it is effective and safe. Nevertheless, electrical stimulation represents a new approach to epilepsy therapy with the potential of eliciting enduring changes in brain function that alter the underlying disease process. Inasmuch as it has been difficult to demonstrate in clinical studies that cur-

rently available symptomatic epilepsy treatments are antiepileptogenic, a fresh strategy is welcome.

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References

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