

IS THERE A “CRITICAL PERIOD” FOR INTERVENTION IN POSTTRAUMATIC EPILEPSY?

A Critical Period for Prevention of Posttraumatic Neocortical Hyperexcitability in Rats

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Penetrating cortical trauma frequently results in delayed development of epilepsy. In the rat undercut model of neocortical posttraumatic hyperexcitability, suppression of neuronal activity by exposing the injured cortex to tetrodotoxin (TTX) *in vivo* for approximately 2 weeks prevents the expression of abnormal hypersynchronous discharges in neocortical slices. We examined the relation between neuronal activity during the latent period after trauma and subsequent expression of hyperexcitability by varying the timing of TTX treatment. Partially isolated islands of rat sensorimotor cortex were treated with Elvax polymer containing TTX to suppress cortical activity and slices obtained for *in vitro* experiments 10 to 15 days later. TTX treatment was either started immediately after injury and discontinued after a variable number of days or delayed for a variable time after the lesion was placed. Immediate treatment lasting only 2 to 3 days, and treatment delayed up to 3 days prevented hyperexcitability. Thus a critical period exists for development of hyperexcitability in this model that depends on cortical activity. We propose that the hyperexcitability caused by partial cortical isolation may represent an early stage of posttraumatic epileptogenesis. A hypothetical cascade of events leading to subsequent pathophysiologic activity is likely initiated at the time of injury but remains plastic during this critical period.

hypothesis is that therapeutic interventions during this critical period can prevent epilepsy. Whether the process of epileptogenesis can be blocked after the initial insult obviously has important conceptual and clinical implications.

This study expands on previous findings by Graber and Prince (1) that tetrodotoxin (TTX), administered after the insult, can reduce the development of epileptiform field potentials in neocortical slices. The investigators extend their earlier work by showing that TTX can reduce the occurrence of epileptiform field potentials, even if the period of TTX exposure is limited to a few days after the insult. Thus Graber and Prince may have identified a period for intervention to block the epileptogenic process with a pharmacologic agent. They have proposed disruption of axon sprouting and the associated formation of abnormal synaptic circuits as a possible mechanism by which TTX blocks activity-dependent epileptogenesis.

One important issue to consider with research aimed at evaluating postinjury therapies designed to block epileptogenesis is whether the proposed therapy directly attenuates the initial injury. Some recent studies, particularly those investigating the epileptogenesis that can occur after status epilepticus, have involved therapy protocols that reduce the initial precipitating injury (i.e., diminish the intensity the status epilepticus). This approach partially nullifies the conceptual basis for a posttraumatic antiepileptogenesis investigation, because blunting the severity of the injury is a different issue from reducing its subsequent epileptogenic effects. Although experimental treatments during an insult could ultimately be useful, such therapies would be practical only in those rare situations in which the patient can be treated during the actual initial insult.

What is needed, instead, is a treatment that can be initiated after the injury. In this study by Graber and Prince, a polymer containing TTX, which was implanted after the undercut injury, prevented the hyperexcitability. It would be informative to examine longer intervals between removal of TTX and the initiation of slice studies to rule out the possibility that TTX delayed, but did not prevent, epileptogenesis. If a critical period also exists for humans (and similarly effective drugs can be used), these findings may translate into clinically important studies. This research exemplifies the type of experimental design that is necessary to evaluate strategies for blocking epileptogenesis after a brain injury.

COMMENTARY

Posttraumatic epilepsy is thought to result from a progressive process that occurs between brain injury and spontaneous recurrent seizures (i.e., epileptogenesis). The experiments in this article by Graber and Prince test the hypothesis that epileptogenesis involves a critical period. A corollary to this

Another critical issue in experimental studies of epileptogenesis is the relation between hyperexcitability and the spontaneous recurrent seizures characteristic of the epileptic state. Many studies seem to assume the equivalence of *hyperexcitability* and *seizure*, implying that hyperexcitability is the same as an increased propensity to generate spontaneous seizures in epileptic brain. Graber and Prince are careful to state that hyperexcitability, as studied in vitro in neocortical slices, may represent a step in the overall mechanism of epileptogenesis, but should not be considered equivalent to the spontaneous recurrent seizures that are the basis of chronic epilepsy. They do hypothesize that hyperexcitability, defined here as periods of repetitive field-potential activity to extracellular stimulation lasting up to tens of seconds, is a functional fingerprint of one part of the overall process of epileptogenesis.

This study highlights the concept of the “critical period,” during which a therapy could potentially be administered to prevent epileptogenesis. Such a therapy would revolutionize clinical care after brain injury. However, a practical therapeutic agent has yet to be identified. Greater understanding of the specific molecular and cellular mechanisms through which cortical networks are modified during epileptogenesis will be required to achieve this goal.

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Reference

1. Graber KD, Prince DA. Tetrodotoxin prevents posttraumatic epileptogenesis in rats. *Ann Neurol* 1999;46:234–242.