

MODELING TRAUMATIC BRAIN INJURY AND POSTTRAUMATIC EPILEPSY

Post-traumatic Epilepsy following Fluid Percussion Injury in the Rat

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The lack of an adequate model of posttraumatic epilepsy (PTE), in which, similar to the human condition, chronic spontaneous focal seizures follow a single episode of traumatic brain injury, has hampered the identification of clinically relevant epileptogenic mechanisms and the development of effective therapies. We studied the electrophysiologic, behavioral, and structural consequences of a clinically relevant model of closed head injury, the lateral fluid percussion injury (FPI), in the rat. We found that a single episode of severe FPI is sufficient to cause PTE. Prolonged electrocorticography (ECoG) demonstrated spontaneous chronic seizures that were partial, originated from the neocortex at the site of injury, and progressively worsened and spread over time. The cases of epilepsy in the posttraumatic population increased over time after injury. Post-FPI epileptic rats exhibited pauses in their behavior, facial automatisms, and myoclonus at the time of epileptiform ECoG events. In vitro local field-potential recordings demonstrated persistent hyperexcitability of the neocortex at and around the site of injury that was associated with intense glial reactivity. These results for the first time demonstrate persistent hyperexcitability of the injured neocortex and define a useful model for pathophysiologic studies of basic mechanisms of spontaneous epileptogenesis and for preclinical screening of effective antiepileptogenic drugs.

studies is not fully understood but may be related to diverse factors, such as the particular characteristics of lesioning, the type and extent of resultant brain injury, the practical constraints of prolonged EEG monitoring, and the difficulty of recognizing and detecting ictal discharge patterns in large volumes of EEG data, with or without available seizure-detection software. Given the obvious clinical importance of an improved mechanistic understanding of the molecular, cellular, and network events involved in posttraumatic epileptogenesis, the time is ripe for reinvigorated efforts to produce a successful animal model of TBI and PTE. With the current availability of several elaborated methods of TBI (e.g., fluid percussion, weight drop, controlled cortical impact) as well as advances in video-EEG recording techniques and analytic programs, an exciting period of discovery may be at hand, as demonstrated by the report of D'Ambrosio et al.

In their recent study, the authors combined the lateral FPI model of TBI in 1-month-old Sprague-Dawley rats with intermittent, extended (4 months) video-electrocorticography (ECoG), via epidural electrode recordings, to determine whether this method of TBI was capable of inducing epileptogenesis and PTE in lesioned animals. They report that FPI successfully resulted in partial seizures, originating proximal to the lesion site, with or without secondary generalization. In assessing electrographic seizure activity, the authors categorized ictal ECoG events to three different grades: grade 1 activity appeared to originate from a focus and was limited to it; grade 2 activity appeared to originate from a focus and then spread; grade 3 activity appeared simultaneously in multiple channels. None of these discharges was recorded in any of the control animals. Lesioned animals typically demonstrated behavioral arrest, facial automatisms, or myoclonus during ictal discharges. These findings are intriguing, given the nature of the electrobehavioral events described, and raise several issues related to the characterization and interpretation of the recorded discharges and accompanying changes in behavior.

A fundamental issue not addressed by the authors is the striking similarity of their recorded discharges to the spontaneous generalized 7- to 9-Hz spike-wave discharges (SWDs) and associated behavioral arrest observed in numerous outbred and inbred strains of common laboratory rats (1), as well as in those strains developed specifically for modeling absence epilepsy (2). In virtually all rodent strains studied, an age-dependent increase

COMMENTARY

Study of the mechanisms of epileptogenesis that follow traumatic brain injury (TBI) has been impeded by the lack of an animal model of posttraumatic epilepsy (PTE). The failure of several investigators to demonstrate PTE in previous animal

in the number of animals demonstrating this phenomenon is seen, including both the number and the duration of the SWDs, which can begin as early as age 40 days (3).

In the study by D'Ambrosio et al., an important consideration related to SWDs is the degree of apparent synchrony noted throughout the discharge. Although these discharges usually have an abrupt and essentially synchronous generalized onset and termination, the patterns are not always so clear cut. Depending on the recording montage, these discharges can appear fragmentary at onset, giving the impression that the discharge initiation is focal rather than generalized; similarly, termination of these discharges can appear asynchronous. Another possible contributor to the apparent increased activity recorded from electrodes proximal to the lesion site is breach rhythm, typically a localized increase in recorded amplitude resulting from the low resistive pathway formed by a skull defect (breach), in this case, the burr hole created for the FPI. In fairness to the authors' report, it is not clear whether either of these issues contributes to the final form of the ECoG traces presented; however, they would seem to merit consideration. With regard to the behavioral arrest and facial automatisms noted during ictal discharges, these findings appear to be very similar to the behavioral semiology observed during SWDs. Interestingly, the myoclonus described in some of the lesioned animals also seems similar to that occurring during partially expressed SWDs (absence events) seen in both control and lesioned Sprague-Dawley animals studied in a different model of neocortical brain injury (4).

Based on the observations noted earlier, the demonstrated injury to cortex and thalamus created by lateral rostral FPI, and the occurrence of simultaneous generalized seizures, a provoca-

tive possibility is that TBI actually resulted in lowering the threshold for the expression of SWDs. If so, the ictal discharges recorded by the authors may represent SWDs rather than, or in addition to, the generation of partial seizures with or without secondary generalization. Because of the importance of the authors' report, additional studies will be required further to delineate and clarify the model's findings. However, the authors' careful, focused study has provided a rich electrophysiologic, anatomic, and behavioral substrate for an improved understanding of the relation between TBI and PTE. Not only does it embody the importance of well-designed animal models for the eventual translation to clinical application, but it also provides a powerful impetus for renewed energy in the field. Comparison of this study's findings with future studies using other models of TBI should provide significant insight into the mechanisms of epileptogenesis and PTE.

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