CURRENT LITERATURE

INSIGHTS INTO THE CELLULAR BASIS OF POSTTRAUMATIC EPILEPSY

Physiological and Structural Evidence for Hippocampal Involvement in Persistent Seizure Susceptibility after Traumatic Brain Injury

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Epilepsy is a common outcome of traumatic brain injury (TBI), but the mechanisms of posttraumatic epileptogenesis are poorly understood. One clue is the occurrence of selective hippocampal cell death after fluid-percussion TBI in rats, consistent with the reported reduction of hippocampal volume bilaterally in humans after TBI and resembling hippocampal sclerosis, a hallmark of temporal-lobe epilepsy. Other features of temporal-lobe epilepsy, such as long-term seizure susceptibility, persistent hyperexcitability in the dentate gyrus (DG), and mossy fiber synaptic reorganization, however, have not been examined after TBI. To determine whether TBI induces these changes, we used a well studied model of TBI by weight drop on somatosensory cortex in adult rats. First, we confirmed an early and selective cell loss in the hilus of the DG and area CA3 of hippocampus, ipsilateral to the impact. Second, we found persistently enhanced susceptibility to pentylenetetrazole-induced convulsions 15 weeks after TBI. Third, by applying $GABA_A$ antagonists during field-potential and optical recordings in hippocampal slices 3 and 15 weeks after TBI, we unmasked a persistent, abnormal APV-sensitive hyperexcitability that was bilateral and localized to the granule cell and molecular layers of the DG. Finally, using Timm histochemistry, we detected progressive sprouting of mossy fibers into the inner molecular layers of the DG bilaterally 2–27 weeks after TBI. These findings are consistent with the development of posttraumatic epilepsy in an animal model of impact head injury, showing a striking similarity to the enduring behavioral, functional, and structural alterations associated with temporal-lobe epilepsy.

Long-Term Hyperexcitability in the Hippocampus After Experimental Head Trauma

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Head injury is a causative factor in the development of temporal lobe epilepsy. However, whether a single episode of concussive head trauma causes a persistent increase in neuronal excitability in the limbic system has not been unequivocally determined. This study used the rodent fluid percussion injury (FPI) model, in combination with electrophysiological and histochemical techniques, to investigate the early (1 week) and long-term (1 month or longer) changes in the hippocampus after head trauma. Low-frequency, single-shock stimulation of the perforant path revealed an early granule cell hyperexcitability in head-injured animals that returned to control levels by 1 month. However, there was a persistent decrease in threshold to induction of seizure-like electrical activity in response to high-frequency tetanic stimulation in the hippocampus after head injury. Timm staining revealed both early- and long-term mossy fiber sprouting at low to moderate levels in the dentate gyrus of animals that experienced FPI. There was a long-lasting increase in the frequency of spontaneous inhibitory postsynaptic currents in dentate granule cells after FPI, and ionotropic glutamate receptor antagonists selectively decreased the spontaneous inhibitory postsynaptic current frequency in the head-injured animals. These results demonstrate that a single episode of experimental closed head trauma induces long-lasting alterations in the hippocampus. These persistent structural and functional alterations in inhibitory and excitatory circuits are likely to influence the development of hyperexcitable foci in posttraumatic limbic circuits.

COMMENTARY

Moderate to severe head trauma is an important risk factor in the development of epilepsy, accounting for up to 13% of ac-

quired epilepsy cases. Clinical studies have shown a relationship between head trauma and temporal lobe epilepsy, but the precise mechanisms underlying the generation of enhanced seizure susceptibility ("epileptogenesis") have not been elucidated. The following key research questions related to posttraumatic epilepsy were addressed in the two recent studies presented here: (1) Does a single episode of traumatic brain injury lead to persistent alterations in seizure threshold? (2) Is brain trauma associated with long-term changes in inhibitory and excitatory networks? (3) Is there anatomical reorganization (mossy fiber sprouting) after brain injury?

The two groups present complementary data by using two somewhat different fluid-percussion injury models (Golarai et al. used weight drop, whereas Santhakumar et al. used atmospheric pressure). It had previously been demonstrated that early seizures occurred within hours of this type of experimental traumatic brain injury and that enhanced seizure susceptibility could be seen for up to 1 week after trauma. None of these prior studies examined whether the reduced seizure threshold persists beyond this initial period, although this is of obvious clinical relevance.

Golarai et al. examined coronal sections obtained from animals sustaining traumatic brain injury to somatosensory cortex 2 to 27 weeks earlier. Focal damage to the neocortex was seen, and in addition, there was progressive and selective loss of hippocampal neurons ipsilateral to the injury. The neurons that were affected included CA3 pyramidal neurons and large hilar cells. This group also found that brain-injured animals had a reduced threshold for induction of seizures by the convulsant pentylenetetrazole. Persistent hyperexcitability was also manifested in dentate gyrus recordings from ipsilateral and contralateral slices obtained from brain-damaged animals. This hyperexcitability was only revealed when single or paired extracellular stimuli were delivered in the presence of $GABA_A$ receptor antagonists, resulting in the triggering of multiphasic field potentials. This result was corroborated in optical recordings with a voltage sensitive dye. Timm staining revealed bilateral mossy fiber sprouting, and this process was noted to progress over the 27 weeks since traumatic brain injury.

Santhakumar et al. showed that within 1 week of trauma, there is hyperexcitability of dentate granule cells in response to low-frequency stimulation of the perforant path due to disinhibition. They found that by 1 to 3 months after trauma, this loss of inhibition recovered. However, a persistent decrease in the seizure threshold was revealed when tetanic stimuli were delivered to the Schaffer collateral system in hippocampal–entorhinal cortex slices from traumatized animals. Tetanic stimulation of slices from control animals induced a primary afterdischarge that lasted for less than 2 minutes, but among slices from brain-injured animals, 44% showed self-sustaining, recurrent epileptiform activity after the first tetanic stimulus. All slices showed seizure-like activity after the third tetanus (vs. only 14% of control slices). Evidence of posttraumatic mossy fiber reorganization matched that of the Golarai et al. study. These authors' examination of spontaneous spike-driven inhibitory postsynaptic currents (IPSCs) is interesting. As expected, within 1 week of brain injury, IPSC frequency was significantly reduced versus control; however, at 5 to 6 months after head injury, IPSC frequency was increased over age-matched controls. Although application of ionotropic glutamate antagonists has little influence over IPSC frequency in control neurons, in cells from brain-damaged animals, exposure to these agents significantly reduced the enhanced frequency at 5 to 6 months. This suggests that increased glutamatergic feedforward excitatory drive onto interneurons supports the posttraumatic increase in net output from the dentate inhibitory network.

Recognizing that each study did have a somewhat different experimental approach and scope, the two articles are largely in accord in their basic findings and conclusions. Persistent susceptibility to hyperexcitability associated with mossy fiber sprouting was clearly demonstrated by both groups. The observations following antagonism of fast inhibition are somewhat at odds with each other (Golarai et al. showed that it revealed hyperexcitability, and Santhakumar et al. showed that it did not). However, they both come to the same conclusion: Inhibition recovers after trauma as a consequence of increased excitatory drive onto inhibitory neurons. One can only wonder whether the acute disinhibition that occurs following brain trauma actually predisposes to the reorganization that ensues and whether early intervention might effectively prevent the process (1,2).

References

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