EPILEPSY CURRENTS

Current Literature

In Basic Science

Neuroinflammation and Seizures After Pediatric Brain Injury: What a Headache!

Interleukin-1 Receptor in Seizure Susceptibility After Traumatic Injury to the Pediatric Brain.

Sample BD, O'Brien TJ, Gimlin K, Wright DK, Kim SE, Casillas-Espinosa PM, Webster KM, Petrou S, Noble-Haeusslein LJ. *J Neurosci* 2017;37:7864–7877.

Epilepsy after pediatric traumatic brain injury (TBI) is associated with poor quality of life. This study aimed to characterize posttraumatic epilepsy in a mouse model of pediatric brain injury, and to evaluate the role of interleukin-1 (IL-1) signaling as a target for pharmacological intervention. Male mice received a controlled cortical impact or sham surgery at postnatal day 21, approximating a toddler-aged child. Mice were treated acutely with an IL-1 receptor antagonist (IL-1Ra; 100 mg/kg, s.c.) or vehicle. Spontaneous and evoked seizures were evaluated from video-EEG recordings. Behavioral assays tested for functional outcomes, postmortem analyses assessed neuropathology, and brain atrophy was detected by *ex vivo* magnetic resonance imaging. At 2 weeks and 3 months post-injury, TBI mice showed an elevated seizure response to the convulsant pentylenetetrazol compared with sham mice, associated with abnormal hippocampal mossy fiber sprouting. A robust increase in IL-1β and IL-1 receptor were detected after TBI. IL-1Ra treatment reduced seizure susceptibility 2 weeks after TBI compared with vehicle, and a reduction in hippocampal astrogliosis. In a chronic study, IL-1Ra-TBI mice showed improved spatial memory at 4 months post-injury. At 5 months, most TBI mice exhibited spontaneous seizures during a 7 d video-EEG recording period. At 6 months, IL-1Ra-TBI mice had fewer evoked seizures compared with vehicle controls, coinciding with greater preservation of cortical tissue. Findings demonstrate this model's utility to delineate mechanisms underlying epileptogenesis after pediatric brain injury, and provide evidence of IL-1 signaling as a mediator of post-traumatic astrogliosis and seizure susceptibility.

Commentary

Significant proportions of patients who suffer moderate to severe traumatic brain injury (TBI) develop posttraumatic epilepsy (PTE) weeks to years after the injury, and approximately 20% of symptomatic epilepsy cases are the result of TBI. Seizures in PTE patients are often medically and surgically intractable, and treatments to prevent development of PTE after a brain injury have not been successful. Preventing posttraumatic epileptogenesis and treating PTE are substantive goals of epilepsy research. Subsequent to the initial damage caused directly by the injury, a myriad of secondary neuropathologies emerge after TBI and may participate in the development of PTE, including, but not limited to, increased cortical excitability, selective cell death, synaptic reorganization, reactive gliosis, increased neurogenesis, altered brain metabolism, and neuroinflammation. In particular, inflammatory cytokines, including the proinflammatory molecule interleukin (IL)-1β, are increased in the brain after TBI or seizures. In rodent models, increased IL-1β levels exacerbate evoked seizures, blocking IL-1 receptors has anticonvulsant effects, and early life inflammation increases seizure susceptibility later in life (1–4), making the IL-1 system a reasonable target to study PTE disease modification. Due to their increased propensity for falls, sports injuries, and accidents, children and adolescents are disproportionately affected by TBI, and development of PTE may be more likely because of the increased vulnerability of the immature brain to postinjury seizures (5) and neuroinflammation (1, 6). Although several studies have suggested that IL-1 receptor blockade might suppress seizures or slow the advancement of epilepsy once it is established, the involvement of the IL-1 system in the initiation and development of PTE or other epilepsies remains murky.

Semple and colleagues addressed these issues using a mouse model of pediatric TBI in which controlled cortical impact (CCI), a focal brain injury that results in PTE when administered to adult mice (7), was used in young mice (postnatal day 21) as a stimulus to induce PTE later in life. This model is useful for studying the process of epileptogenesis, since the trigger for epilepsy development is temporally and spatially well defined. The authors then determined if a pharmacologic blockade of IL-1 receptors, beginning shortly after injury, modified the initial processes of epilepsy development and cognitive recovery after pediatric brain injury. Among the more

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interesting findings was that CCI in young mice resulted in a large proportion that developed spontaneous seizures later in life (~95%), relative to the prevalence reported after CCI injury in adults (9–50%) (7–9). Speculatively, this greatly increased propensity for PTE development after pediatric TBI could be related to inflammatory priming in the immature brain. During a seven-day EEG monitoring period, however, the proportion of mice that developed PTE was not significantly affected by prophylactic treatment with an IL-1 receptor antagonist (IL-1Ra) postinjury. Although spontaneous seizure development was unaffected, a brief IL-1Ra treatment paradigm after TBI did reduce the severity of chemically induced seizures evoked two weeks after CCI. Seizures evoked at six months after continuous, postinjury IL-1Ra treatment were also attenuated. Spatial memory deficits were also detected at three months postinjury, and treatment with IL-1Ra abrogated these memory deficits. IL-1β protein was increased in brain within hours after TBI, and in serum shortly thereafter, coincident with early and sustained astroglial activation, suggesting an astroglial source of IL-1β. The astrogliosis was attenuated by treatment with IL-1RA. Reducing the effects of IL-1 receptor activation by blocking receptors shortly after TBI, thus significantly improved behavioral and cellular changes associated with epileptogenesis and attenuated evoked seizure severity, all of which suggests that blocking inflammatory cytokine signaling after TBI interferes with components of the epileptogenic process. In contrast, and possibly separately, development of spontaneous seizures after TBI evidently involves additional mechanisms, and these could include other aspects of neuroinflammation, altered brain metabolism, synaptic reorganization, or other injury-induced processes that have been hypothesized to lead to spontaneous seizure development. The findings regarding the IL-1 system are consistent with the previously proposed hypothesis that inflammatory processes contribute to at least some aspects of injury-induced neuropathology that supports seizure generation and epilepsy co-morbidities (4).

Critically, the postinjury development of spontaneous seizures was not affected by IL-1 receptor blockade. This highlights a fundamental question in the quest for an anti-epileptogenic treatment for PTE: what is epileptogenesis? Canonically, epileptogenesis is defined as the gradual process by which a healthy brain develops epilepsy, a chronic condition in which spontaneous seizures occur. Relatively recently, it has been proposed that the definition of epileptogenesis should evolve to include not only the prodromal processes occurring during the development of epilepsy, but also those that exacerbate epilepsy phenotypes after spontaneous seizures emerge (10). There is virtue in this assertion, because seizures beget seizures, and epilepsy has come to be acknowledged as a progressive disorder in this regard. A primary aim of epilepsy research, however, remains the outright prevention of epilepsy development and we should not lose sight of that goal. The process of epileptogenesis involves a constellation of cellular and brain system changes, and it is probably naïve to believe that a single treatment will fully prevent posttraumatic epileptogenesis—either before or after spontaneous seizures commence. Hence, the authors found that neuroinflammatory processes involving IL-1 signaling appear to contribute to at least some pathologic changes in brain function associated with increased evoked seizure susceptibility in mice with PTE, but blocking those processes does not prevent PTE itself. To rephrase, blocking the activity of IL-1 receptors after TBI has potential anti-epileptogenic effects, but does not ultimately affect PTE development. Broadly, these results reinforce the notion that fundamental differences may exist in the processes underlying evoked versus spontaneous seizure susceptibility as related to epileptogenesis. Still, there is intrinsic value in identifying any aspect of epilepsy development, and more effective treatments for reducing seizure frequency and severity may arise from understanding these processes. The work of Semple and colleagues advances that aim by extending our understanding of the contribution of neuroinflammatory processes to seizure susceptibility and cognitive recovery after pediatric brain injury. Building upon this knowledge to identify and account for mechanisms that contribute to the development of spontaneous seizures subsequent to TBI or other insult will be critical for developing treatments to prevent epileptogenesis, canonically defined.

by Bret N. Smith, PhD

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