EPILEPSY CURRENTS

Current Literature

In Basic Science

Turning Up the Heat on Endocannabinoid Signaling

Transient Increase of Interleukin-1β After Prolonged Febrile Seizures Promotes Adult Epileptogenesis Through Long-Lasting Upregulating Endocannabinoid Signaling.

Feng B, Tang Y, Chen B, Xu C, Wang Y, Dai Y, Wu D, Zhu J, Wang S, Zhou Y, Shi L, Hu W, Zhang X, Chen Z. *Sci Rep* 2016;6:21931.

It remains unclear how infantile febrile seizures (FS) enhance adult seizure susceptibility. Here we showed that the transient increase of interleukin-1β (IL-1β) after prolonged FS promoted adult seizure susceptibility, which was blocked by interleukin-1 receptor antagonist (IL-1Ra) within a critical time window. Postnatal administered IL-1β alone mimicked the effect of FS on adult seizure susceptibility. IL-1R1 knockout mice were not susceptible to adult seizure after prolonged FS or IL-1β treatment. Prolonged FS or early-life IL-1β treatment increased the expression of cannabinoid type 1 receptor (CB1R) for over 50 days, which was blocked by IL-1Ra or was absent in IL-1R1 knockout mice. CB1R antagonist, knockdown and endocannabinoid synthesis inhibitor abolished FS or IL-1β-enhanced seizure susceptibility. Thus, this work identifies a pathogenic role of postnatal IL-1β/IL-1R1 pathway and subsequent prolonged prominent increase of endocannabinoid signaling in adult seizure susceptibility following prolonged FS, and highlights IL-1R1 as a potential therapeutic target for preventing the development of epilepsy after infantile FS.

Commentary

Febrile seizures (FSs) are the most common seizures in childhood, with a prevalence of approximately 3 to 5 percent in Europe and North America. While simple FSs (lasting under 15 minutes) are generally not associated with an increased risk of developing epilepsy, there is a growing body of clinical and experimental evidence that prolonged early-life FSs are epileptogenic and lead to long-term alterations of neuronal function and excitability (1, 2). The clinical impact of early-life prolonged FSs is evident from retrospective studies that demonstrate a history of complex FSs in patients with mesial temporal lobe epilepsy (3, 4). A history of early-life prolonged FSs is also common in disorders such as Dravet syndrome, raising the possibility that they may also influence disease progression in these patients. Thus, identifying the underlying mechanisms by which these early-life seizure events alter neuronal function could uncover novel targets for therapeutic intervention, and is therefore of considerable clinical and research interest.

Advances in our understanding of the molecular and neuronal changes that occur following prolonged FSs have relied largely on the use of experimental FS paradigms in mice and rats. In most published studies, prolonged early-life FSs are modeled by subjecting juvenile rodents to approximately 30 minutes of hyperthermia via an external heat source in order to raise core and brain temperatures to approximately 41 to 43°C (2). Using this approach, a number of earlier studies found upregulation of the proinflammatory cytokine interleukin (IL)-1β (1) and altered endocannabinoid signaling (5) following prolonged experimental FSs. In the present study, Feng and colleagues further explored the contribution of IL-1β and the cannabinoid type 1 receptor (CB1R) to epileptogenesis following prolonged hyperthermia.

In agreement with other studies, Feng and colleagues first observed that 8-day-old rat pups subjected to 30 minutes of hyperthermia displayed greater susceptibility to induced seizures in adulthood. Examination of IL-1β protein levels revealed a transient increase 12 hours after hyperthermia, with a return to baseline after 24 hours. Interestingly, the administration of IL-1β to 8-day-old mice, in the absence of hyperthermia, also led to increased seizure susceptibility in adulthood. Furthermore, the effect of early-life hyperthermia on adult seizure susceptibility was prevented by blocking IL-1β signaling within 12 hours of hyperthermia. Taken together, these results provide support for the contribution of IL-1β to the epileptogenic process. However, these results also raise an important question: how does a transient increase in IL-1β levels lead to the long-term effects of early-life hyperthermia? While this complex question is unlikely to be answered by a single mechanism, the findings of Feng and colleagues appear to provide one piece of the puzzle. Specifically, the authors observed that CB1R was upregulated 3 days after hyperthermia and elevated levels persisted into adulthood. Importantly, the authors showed that the early-life administration of IL-1β resulted in higher CB1R levels in adulthood, pointing to a mechanistic link between the transient increase in IL-1β levels and long-term CB1R upregulation. Furthermore, reducing IL-1β

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signaling immediately after prolonged hyperthermia prevented the rise in CB1R expression. Finally, the authors found that the increase in adult seizure susceptibility due to prolonged early-life hyperthermia could be blocked by the administration of a single dose of the CB1R antagonist SR141716A one week after hyperthermia. Interestingly, SR141716A was not protective when administered 14 days after hyperthermia. In contrast, the administration of a CB1R agonist reversed the protective effect of the recombinant human IL1 receptor antagonist (IL-1Ra) on adult seizure susceptibility. CB1R was also found to be increased in the epileptic foci of temporal lobe epilepsy (TLE) patients with a history of FSs when compared with TLE patients without a history.

The results of Feng and colleagues provide further evidence for the link between IL-1β and CB1R upregulation following prolonged early-life hyperthermia and highlight the contribution of these changes to epileptogenesis. Importantly, these results also suggest that pharmacological modulation of neuroinflammation and/or endocannabinoid signaling may provide avenues for therapeutic intervention. However, based on the findings of this study, treatment efficacy might be influenced by the timing of drug administration relative to FS occurrence. In contrast to evidence for the role of CB1R in epileptogenesis following prolonged FSs, the administration of SR141716A did not affect the development of spontaneous recurrent seizures after kainate-induced status epilepticus in adult rats (6). Genetic deletion of CB1R also did not affect epileptogenesis in the kindling paradigm (7). Thus, additional studies will be required to establish whether endocannabinoid signaling is likely to provide a broad target for the treatment of epilepsy.

It is clear that further research is required to develop a comprehensive understanding of the long-term effects of prolonged early-life FSs on brain development. For example, a recent study revealed large scale alterations in gene expression following prolonged experimental FSs, implying the involvement of multiple pathways (8). Accordingly, other mechanisms, such as modification of h-channels (9) and the impairment of interastrocytic gap junction coupling (10), have also been proposed as possible links between early-life FSs and epilepsy development. Given the findings of Feng and colleagues, evaluating the potential contribution of the CB2R receptor to the long-term effects of early-life FSs should also be explored. Finally, while the use of prolonged hyperthermia in juvenile rodents has provided valuable information, clearly this model does not fully match the clinical processes that lead to FS generation; development of better models is therefore warranted. Similarly, while more technically challenging and time consuming, the evaluation of spontaneous seizure development and frequency, rather than susceptibility to induced seizures, will likely provide a much better measure of epileptogenesis.

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