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COMMENTARY

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Experimental status epilepticus, COX-2 and BDNF: Connecting the dots

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Brain and peripheral inflammation and immune pathways play distinct roles in a variety of epilepsies. Disease modification(s) and reduction in seizure burden by targeting specific pro-inflammatory mediators have represented a demanding and controversial quest.[1–3] Within this realm, the inducible cyclooxygenase-2 (COX-2) and brain-derived neurotrophic factor (BDNF), and their signaling cascades, were proposed as relevant candidate entry points in central nervous system (CNS) disorders.[2,4–6] COX-2 is upstream to, and controls, a broad inflammatory pathway leading to the production of prostaglandin E2 (PGE2). As COX-2 brain expression increases during seizures, the effectiveness of COX-2 inhibitors has been tested with varying outcomes.[2]

Here, Yu and Jiang have outlined previously missing links and the temporal dynamics of COX-2 and BDNF expression in the hippocampus in response to status epilepticus (SE).[7] To avoid possible model-specific biases, they elicited experimental SE by injecting either KA or pilocarpine in rodents. With a panel of molecular biology tools, they showed that, in the hippocampus, the induction of COX-2 temporally preceded that of BDNF and that blocking COX-2 activity with a specific inhibitor (SC-58125) prevented the BDNF surge post-SE. Next, in proceeding to validate their hypothesis: i) They found that PGE2, a key COX-2 product, was sufficient to promote BDNF secretion from hippocampal cells; and ii) they targeted the PGE2 receptor EP2 by using a selective, brain-permeable antagonist (TG6-10-1) that subsequently decreased downstream BDNF and TrkB (BDNF receptor) signaling in the hippocampus post-SE. From these data, they conclude that, after experimental SE, COX-2 controls BDNF/TrkB signaling via PGE_2/EP2. Because the EP2 antagonist TG6-10-1 reduced BDNF/TrkB signaling, the authors propose this pharmacological strategy to limit the inflammatory pathophysiology typical of post-SE in these models.

These results support the general concept that an early and targeted pharmacological intervention after an acute brain insult (here SE[8]) may curb the pathological sequel over time, here epileptogenesis leading to spontaneous seizures. Because of the post-SE rapidly evolving pathophysiological traits, identifying or targeting a specific culprit is challenging, particularly when it comes to inflammation and the varying, even contrasting, roles that specific cell types or soluble factors may have as a function of time, brain regions, and tissue lesion. Furthermore, when considering specific factors and their receptors, the extent of supra-threshold stimulation(s) should be considered. Thus, the activation of BDNF is required for a variety of physiological processes including learning and memory,[9] while an excessive BDNF/TrkB interplay, or activation, plays a pathological role in certain brain diseases including epilepsies.[4] These delicate and varying equilibriums need to be controlled when planning the ensuing large-scale (pre)clinical trials and in case of clinical applications, along with a methodical examination of systemic and brain unwanted side effects associated with pro- or anti-inflammatory modifications or adaptations.[1,10–12]

In conclusion, this work connects COX-2 activation to BDNF/TrkB and PGE2/EP2 in the hippocampus after experimental SE. The authors propose the use of a brain-permeable antagonist as a strategy to suppress the abnormal BDNF/TrkB activity with a hypothesized preclinical application to post-insult settings.

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None.

CONFLICTS OF INTEREST

I have no conflicts to disclose. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Radu BM, Epureanu FB, Radu M, Fabene PF, Bertini G, et al. Nonsteroidal anti-inflammatory drugs in clinical and experimental epilepsy. Epilepsy Res. 2017;131:15–27.
2. Rojas A, Jiang J, Ganesh T, Yang M-S, Lelutiu N, Gueorguieva P, et al. Cyclooxygenase-2 in epilepsy. Epilepsia. 2014;55:17–25.
3. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. Nat Rev Neurol. 2011;7:31–40.
4. Fernández-García S, Sancho-Balsells A, Longueville S, Hervé D, Gruart A, Delgado-García JM, et al. Astrocytic BDNF and TrkB regulate severity and neuronal activity in mouse models of temporal lobe epilepsy. Cell Death Dis. 2020;11:411.
5. Liu Q, Liang X, Wang Q, Wilson EN, Lam R, Wang J, et al. PGE2 signaling via the neuronal EP2 receptor increases injury in a model of cerebral ischemia. Proc Natl Acad Sci U S A. 2019;116:10019–24.
6. Zhu X, Yao Y, Yang J, Zhengxie J, Li X, Hu S, et al. COX-2-PGE2 signaling pathway contributes to hippocampal neuronal injury and cognitive impairment in PTZ-kindled epilepsy mice. Int Immunopharmacol. 2020;87:106801.
7. Yu Y, Jiang J. COX-2/PGE2 axis regulates hippocampal BDNF/TrkB signaling via EP2 receptor after prolonged seizures. Epilepsia Open. 2020;5:418–31.
8. Klein P, Dingledine R, Aronica E, Bernard C, Blümcke I, Boison D, et al. Commonalities in epileptogenic processes from different acute brain insults: Do they translate? Epilepsia. 2018;59:37–66.
9. Minichiello L. TrkB signalling pathways in LTP and learning. Nat Rev Neurosci. 2009;10:850–60.
10. Marchi N, Johnson AJ, Puvenna V, Johnson HL, Tierney W, Ghosh C, et al. Modulation of peripheral cytotoxic cells and ictogenesis in a model of seizures. Epilepsia. 2011;52:1627–34.
11. Rana A, Musto AE. The role of inflammation in the development of epilepsy. J Neuroinflammation. 2018;15:144.
12. Zub E, Canet G, Garbelli R, Blaquiere M, Rossini L, Pastori C, et al. The GR-ANXA1 pathway is a pathological player and a candidate target in epilepsy. FASEB J. 2019;33:13998–4009.

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