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EDITORIAL

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An interview with Ying Yu, 2021 *Epilepsia Open* Prize Winner for Basic Science Research

1 | WHO ARE YOU?

I am a research scientist at the University of Tennessee Health Science Center College of Pharmacy. My current research work focuses on neuroinflammation and neurodegeneration in CNS conditions such as epileptic seizures. I obtained my BS in Biochemistry from East China University of Science and Technology in Shanghai and PhD in Chemistry (Biomolecular) from Emory University in Atlanta. I received research training at Emory University School of Medicine as a postdoctoral fellow and Cincinnati Children's Hospital Medical Center as a research associate.

2 | WHAT GOT YOU INTERESTED IN EPILEPSY RESEARCH?

As an undergraduate student, I conducted my thesis research in Shanghai Institute of Biochemistry and Cell Biology of the Chinese Academy of Sciences from 1998 to 1999. We were trying to elucidate the roles of γ-aminobutyric acid transporters (GATs) in epilepsy and other neurological complications. My work specifically contributed to findings that the overexpression of GAT subtype 1 (GAT1) in mice increased the susceptibility of animals to kainic acid–induced seizures and led to cognitive deterioration.[1] This early research training not only resulted in two coauthor publications[1,2] but also played a major role in my current scientific research interest in epilepsy.

3 | EXPLAIN FOR OUR GENERAL READERSHIP WHAT QUESTION YOUR STUDY ADDRESSED AND HOW DID YOU GO ABOUT DESIGNING YOU STUDY?

Despite marked advances in seizure treatment during the past few decades, there are still more than 30% of epilepsy patients who do not adequately respond to the current frontline medications. It is another very unfortunate fact that current antiseizure drugs (ASDs) merely provide symptomatic relief, and no US FDA-approved drug has yet been demonstrated to prevent the development of disease or modify its progression. A major obstacle to the identification of novel antiepileptic and potentially antiepileptogenic targets is that the molecular mechanisms whereby a normal brain is transformed to one that generates unprovoked recurrent seizures after initial precipitating incidents remain unsolved.

Accumulating evidence from preclinical studies during the past two decades suggests that the abnormal excessive brain-derived neurotrophic factor (BDNF) signaling via its tropomyosin-related kinase receptor B (TrkB) is requisite to acquired forms of epilepsy of various etiologies.[3,4] It thus has been widely proposed that blocking BDNF/TrkB signaling or the downstream effector phosphoinositide-specific phospholipase C-γ1 (PLC-γ1) might provide promising strategies to interrupt acquired epileptogenesis.[5,6] However, a key unsolved puzzle is the upstream signaling events that are immediately triggered by precipitating events such as status epilepticus (SE) and directly promote hippocampal BDNF/TrkB activation, thereby stimulating epileptogenesis.

4 | WHAT WERE THE RESULTS AND HOW DO YOU INTERPRET YOUR FINDINGS?

In this work,[7] we showed that cyclooxygenase-2 (COX-2) and BDNF in the hippocampus were rapidly upregulated in very similar time-dependent manners after the onset of SE, while the induction of COX-2 temporally and quantitatively led that of BDNF. Blocking COX-2 enzymatic activity by selective inhibitor prevented BDNF elevation in the hippocampus following SE. As a dominant COX-2 product in the brain, prostaglandin E2 (PGE_2) alone was sufficient to stimulate hippocampal cells to synthesize and secrete BDNF, suggesting that a PGE_2 signaling pathway might be directly involved in hippocampal BDNF production. We further found that

inhibiting the $G\alpha_s$-coupled PGE_2 receptor EP2 by a selective small-molecule antagonist decreased the SE-triggered phosphorylation of the cAMP response element-binding protein (CREB) and activation of the BDNF/TrkB signaling in the hippocampus. However, our results also show that EP2 receptor inhibition did not fully prevent the SE-elevated BDNF in the hippocampus, nor did it completely revert the phosphorylation of CREB and TrkB in the same brain area after SE, suggesting that some other yet-to-be-identified mechanism might also play a role.

5 | WHAT NEXT STEPS IN EPILEPSY RESEARCH ARE YOU TAKING AND WHAT ARE YOUR CAREER GOALS?

TrkB and its downstream effectors emerged as appealing targets for preventing or suppressing acquired forms of epilepsy, but molecular mechanisms whereby BDNF/TrkB signaling is upregulated in the hippocampus following initial precipitating events largely remain unknown. Our findings suggest that COX-2 via PGE_2/EP2 signaling pathway regulates hippocampal BDNF/TrkB activity following prolonged seizures. EP2 inhibition by selective small-molecule antagonists might therefore provide a novel strategy to suppress abnormal TrkB activity during acquired epileptogenesis. However, future studies are required to test this hypothesis using a combination of pharmacological and genetic approaches. Hopefully, our follow-on research will help to identify some novel molecular targets that are druggable for new antiepileptic and/or antiepileptogenic therapies.

6 | WHAT DOES THE *EPILEPSIA OPEN* PRIZE MEAN FOR YOU, YOUR LABORATORY, RESEARCH INSTITUTE, AND YOUR FUTURE?

It is truly an honor to receive the Basic Science *Epilepsia Open* Prize for 2021. I am very grateful to Editors of *Epilepsia Open*, Members of Editorial Board, and the ILAE President for their recognition of our research work. I also want to thank people who work in our laboratory for their support. With this encouragement, I am very much looking forward to continuing my current drug discovery research in epilepsy and sharing our future exciting findings on *Epilepsia Open* and other journals and platforms sponsored by the ILAE.

Read the winning article "COX-2/PGE2 axis regulates hippocampal BDNF/TrkB signaling via EP2 receptor after prolonged seizures."

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