IL-1-PIP3 signal cascade mediates epilepsy and sleep disturbances

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Abstract

Objectives: Interleukin-1β (IL-1β) serves as a prominent factor in the central nervous system for the inflammatory process, initiating a signaling cascade via phosphatidylinositol 3-kinase (PI3K). Within the PI3K pathway, two crucial membrane phospholipids play the significant role, including phosphatidylinositol (4,5)-bisphosphate (PIP2) and phosphatidylinositol (3,4,5)-trisphosphate (PIP3). While prior research has uncovered certain effects of PIP2 in epileptogenesis, the role of PIP3 remains unclear. In our study, we employed PTZ-induced epileptic mice to explore the roles of PIP3 in epileptogenesis and its impact on epilepsy-induced sleep disruptions.

Methods: Our hypothesis proposed a pivotal role for PIP3 in the molecular mechanism of seizures. To test this hypothesis, we intraperitoneal administered low dose of PTZ, once every two days for seven injections, to induce the spontaneous recurrent seizures in mice. We then analyzed sleep patterns and monitored the generation of epileptic spikes through EEG recordings. Our study used IL-1R1 knockout (KO) and wild-type mice to distinguish the differences in seizure generation and sleep structure. Additionally, we employed various inhibitors to block specific signaling pathways to further prove our hypothesis.

Results: Our findings emphasized the substantial role of IL-1β and PIP3 in epileptogenesis, suggesting that interventions aimed at these pathways could alleviate PTZ-induced seizures and the sleep disturbances. To further elucidate the signaling cascade within this pathway, we conducted Western blot analysis to quantify alterations of protein expression. The results revealed the significant effects on the protein expression levels of interaction protein for cytohesin exchange factors 1 (IPCEF1, the PIP3 binding protein) and NMDA receptor (NMDAR) subunits. Furthermore, our EEG recording data allowed us to discern the changes in sleep-wake architecture and assess sleep quality. We also observed that the blockade of this pathway may have an impact on sleep in epilepsy.

Conclusion: In summary, our study suggests that PTZ kindling increases IPCEF1 and NMDAR NR1 subunit expression. Interestingly, using inhibitors and antagonists as

treatments mitigated the increase induced by PTZ. These results further validated the involvement of the IL-1/PIP3/AKT signaling pathway and highlighted the significance of PIP3 in epilepsy. This pathway may be a potential research avenue for treating epilepsy, warranting further in-depth investigation in future studies.