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Letter to the Editor

Organoid-based Studies in Targeted Therapy for Epilepsy

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Dear Editor,

The inability to control seizures in approximately one third of patients with epilepsy despite the current anti-epileptic drug treatments has brought the development of new approaches that target the pathophysiological mechanisms of epilepsy into focus.[1,2] In this context, I have read with great interest the articles "The S100B Protein in Epilepsy" and "A New Strategy in Epilepsy Therapy through Attenuation of Phosphorylated Tau and Amyloid-Beta" published in your journal that provide some important insights into different molecular mechanisms that may contribute to neuronal injury, neuroinflammation and neurodegenerative processes in epilepsy.[2,3]

In their review, Khotib and Maizan[3] highlight the cellular mechanisms involving the mammalian target of rapamycin-mediated tau kinases and phosphatases that are activated by repeated neuronal stimulation, leading to oligomerization and clustering of p-tau and amyloid-beta (Aβ) fibrils. Hyperphosphorylated tau has been hypothesized to interfere with microtubule stability and impair axonal transmission, while Aβ accumulation has been proposed to impair synaptic signaling. It can be hypothesized that this condition may induce irreversible alterations at both cellular and synaptic levels over time, diminishing antiepileptic drug responsiveness.[3] Seçen et al.[2] reported that its high levels in the blood and cerebrospinal fluid after a seizure could be a marker of inflammatory response and neuronal injury. Recurrent epileptic activity leads to increased S100B release and a neuroinflammatory response through oxidative stress, blood-brain barrier breakdown, and neuroglial activation. This elevated environment of neuronal stress can induce neurodegenerative processes, such as tau phosphorylation and alterations in amyloid metabolism. Current evidence does not demonstrate that S100B directly induces tau or Aβ pathology. Moreover, clinical research has predominantly targeted tau- and amyloid-targeted medications, with limited evidence for S100B-targeted treatments.[2,3]

With this letter, I seek to emphasize the contribution that approaches based on human-derived brain organoids can make to understanding the mechanisms underlying the pathogenesis of epilepsy and to determining targeted treatment strategies.

Organoids are three-dimensional cellular structures generated in vitro from pluripotent stem cells; they can be differentiated into specific cell types and tissues. Using stem cell and bioengineering methods, these structures can be engineered to mimic human brain tissue.[1] These models are employed in a variety of fields such as modeling diseases, investigating unknown genetic variants, drug development and testing of therapeutic candidates.[4] In this context, it is possible to study the bidirectional relationship between S100B signal modulation and tau/Aβ metabolism and its effect on neuronal functions. This could provide insights about causal links between these molecular pathways and epileptiform neuronal activity and assess their influence on electrical activity at the network level.[4,5] In addition, it guides the development of personalized therapies through the assessment of phenotype-specific therapeutic responses.

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