Fingolimod

Temporal lobe epilepsy (TLE) represents a devastating neurological condition, in which approximately 4/5 of patients remain refractory for anti-convulsive drugs. Epilepsy surgery biopsies often reveal the damage pattern of "hippocampal sclerosis" (HS) characterized not only by neuronal loss but also pronounced astrogliosis and inflammatory changes. Since TLE shares distinct pathogenetic aspects with multiple sclerosis (MS), we have here scrutinized therapeutic effects in experimental TLE of the immunmodulator fingolimod, which is established in MS therapy. Fingolimod targets sphingosine-phosphate receptors (S1PRs). mRNAs of fingolimod target S1PRs were augmented in two experimental post status epilepticus (SE) TLE mouse models (suprahippocampal kainate/pilocarpine). SE frequently induces chronic recurrent seizures after an extended latency referred to as epileptogenesis. Transient fingolimod treatment of mice during epileptogenesis after suprahippocampal kainate-induced SE revealed substantial reduction of chronic seizure activity despite lacking acute attenuation of SE itself. Intriguingly, fingolimod exerted robust anti-convulsive activity in kainate-induced SE mice treated in the chronic TLE stage and had neuroprotective and anti-gliotic effects and reduced cytotoxic T cell infiltrates. Finally, the expression profile of fingolimod target-S1PRs in human hippocampal biopsy tissue of pharmacoresistant TLE patients undergoing epilepsy surgery for seizure relief suggests repurposing of fingolimod as novel therapeutic perspective in focal epilepsies [1)].

Excessive inflammation after traumatic brain injury (TBI) is a major cause of secondary TBI. Though several inflammatory biomarkers have been postulated as the risk factors of TBI, there has not been any comprehensive description of them. Fingolimod, a new kind of immunomodulatory agent which can diminish various kinds of inflammatory responses, has shown additional therapeutic effects in the treatment of intracranial cerebral hematoma (ICH), ischemia, spinal cord injury (SCI), and many other CNS disorders. However, its therapeutic application has not been confirmed in TBI. Thus, we hypothesized that a 3-day consecutive fingolimod administration could broadly modulate the inflammatory reactions and improve the outcomes of TBI. The TBI models of C57/BL6 mice were established with the controlled cortical impact injury (CCI) system. A 3-day consecutive fingolimod therapy (given at 1, 24, and 48 h post injury) was performed at a dose of 1 mg/kg. The flow cytometry, immunoflourence, cytokine array, and ELISA were all applied to evaluate the immune cells and inflammatory markers in the injured brains. Immunohistochemical staining with anti-APP antibody was performed to assess the axonal damage. The neurological functions of these TBI models were assessed by mNSS/Rota-rod and Morris water maze (MWM). The brain water content and integrity of the blood-brain barrier (BBB) were also observed. On the 3rd day after TBI, the accumulation of inflammatory cytokines and chemokines reached the peak and administration of fingolimod reduced as many as 20 kinds of cytokines and chemokines. Fingolimod decreased infiltrated T lymphocytes and NK cells but increased the percentage of regulatory T (Treg) cells, and the concentration of IL-10 on the 3rd day after TBI. Fingolimod also notably attenuated the general activated microglia but augmented the M2/M1 ratio accompanied by decreased axonal damage. The neurological functions were improved after the fingolimod treatment accompanied with alleviation of the brain edema and BBB damage. This study suggests that the 3-day consecutive fingolimod administration extensively modulates multiple immuno-inflammatory responses and improves the neurological deficits after TBI, and therefore, it may be a new approach to the treatment of secondary TBI [2)].

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