Cerebral ischemia-reperfusion injury

Cerebral ischemia reperfusion injury, is the tissue damage caused when blood supply returns to the tissue after a period of ischemia or lack of oxygen. The absence of oxygen and nutrients from blood during the ischemic period creates a condition in which the restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress rather than restoration of normal function.

Despite successful revascularization, reperfusion after prolonged ischemia causes ischemia reperfusion (I/R) injury.

Pathogenesis

Cranioplasty-related reperfusion injury

Studies have shown that the medical community has paid the role of inflammation and pyroptosis in cerebral ischemia-reperfusion injury more and more attention.

Caspase-1 was found to play a vital role in regulating inflammation pathways and pyroptosis in many inflammation-associated diseases, especially in cerebral ischemia-reperfusion injury. Not only that, Caspase-1 inhibitors have been shown to reduce the damage of cerebral ischemia-reperfusion injury by inhibiting inflammation and pyroptosis. And the Caspase-1 inhibitor, Belnacasan, has been proved to modify the active site of Caspase-1 and lead to the blocking of Caspase-1, thus correlating with tissue protection of inflammatory diseases in animal models. Therefore, it's essential to screen and design potential Caspase-1 inhibitors to reduce cerebral ischemia-reperfusion injury and protect brain function by reducing inflammation and pyroptosis, which provides a new idea for clinical treatment of the cerebral ischemia-reperfusion injury. This study applied a group of computer-aided technology, such as Discovery Studio 4.5, Schrodinger, and PyMol, to screen and assess potential Caspase-1 inhibitors. Moreover, the ADME (absorption, distribution, metabolism, excretion) and TOPKAT (Toxicity Prediction by Computer Assisted Technology) molecules of Discovery Studio 4.5 were conducted to evaluate molecules' pharmacological and toxicological features. Then, precise molecular docking was applied to assess the binding mechanism and affinity between Caspase-1 and selected compounds. Besides, molecular dynamics simulations were performed to determine the stability of ligand-receptor complexes in the natural environment. In summary, this study lists promising drug candidates and their pharmacological properties, promoting the development of Caspase-1 inhibitors and deepening the understanding of the interaction between inhibitors and Caspase-1 [1)]

Mitochondrial fragmentation drastically regulates mitochondrial homeostasis in brain illness. However, the role of mitochondrial fragmentation in cerebral ischemia reperfusion injury remains unclear. Nur77, a regulator of mitochondrial homeostasis, is associated with heart and liver IR injury, but its effects on mitochondrial function in cerebral IR injury has not been studied intensively.

Pathophysiology

Lysosomal-associated transmembrane protein 5 (LAPTM5) has been demonstrated to be involved in regulating immunity, inflammation, cell death, and autophagy in the pathophysiological processes of many diseases. However, the function of LAPTM5 in cerebral ischemia-reperfusion (I/R) injury has not yet been reported. In this study, we found that LAPTM5 expression was dramatically decreased during cerebral I/R injury both in vivo and in vitro. LAPTM5 knockout (KO) mice were compared with a control, and they showed a larger infarct size and more serious neurological dysfunction after transient middle cerebral artery occlusion (tMCAO) treatment. In addition, inflammatory response and apoptosis were exacerbated in these processes. Furthermore, gain- and loss-of-function investigations in an in vitro model revealed that neuronal inflammation and apoptosis were aggravated by LAPTM5 knockdown but mitigated by its overexpression. Mechanistically, combined RNA sequencing and experimental verification showed that the apoptosis signal-regulating kinase 1 (ASK1)-c-Jun N-terminal kinase (JNK)/p38 pathway was mainly involved in the detrimental effects of LAPTM5 deficiency following I/R injury. Specifically, LAPTM5 directly interacts with ASK1, leading to decreased ASK1 N-terminal dimerization and the subsequently reduced activation of downstream JNK/p38 signaling. In conclusion, LAPTM5 was demonstrated to be a novel modulator in the pathophysiology of brain I/R injury, and targeting LAPTM5 may be feasible as a stroke treatment [2)].

Treatment

Cerebral ischemia-reperfusion injury Treatment.

Outcome

Reperfusion triggers cell death through generation of mitochondrial reactive oxygen species (mROS) [3)].

Ischemia-reperfusion injury (IRI) is an important cause of adverse prognosis after recanalization in patients with acute occlusion of major intracranial artery (AOMIA).

Cerebral ischemia-reperfusion injury is one of the most severe diseases in terms of mortality and disability, which seriously threatens human life and health.

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