Caspase-1 inhibitor

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, a syudy of Li et al. 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)].

Inflammatory Caspase-1 has a significant impact on AD-like pathophysiology and Caspase-1 inhibitor, VX-765, reverses cognitive deficits in AD mouse models. Here, a one-month pre-symptomatic treatment of Swedish/Indiana mutant amyloid precursor protein (APPSw/Ind) J20 and wild-type mice with VX-765 delays both APPSw/Ind- and age-induced episodic and spatial memory deficits. VX-765 delays inflammation without considerably affecting soluble and aggregated amyloid beta peptide (Aβ) levels. Episodic memory scores correlate negatively with microglial activation. These results suggest that Caspase-1-mediated inflammation occurs early in the disease and raise hope that VX-765, a previously Food and Drug Administration-approved drug for human CNS clinical trials, may be a useful drug to prevent the onset of cognitive deficits and brain inflammation in AD [2)].

Results indicate that caspase-1 could amplify the plural inflammatory responses in the ICH. Administration of Ac-YVAD-cmk has the potential to be a novel therapeutic strategy for ICH [3)].

Herpes simplex virus (HSV) vectors expressing caspase inhibitors p35 and crmA have been shown to be neuroprotective against various excitotoxic insults. Here we further evaluated the possible neuroprotective role of p35 and crmA in a rat stroke model. Overexpression of p35, but not crmA, significantly increased neuronal survival. Results of double immunofluorescence staining indicate that compared with neurons infected with crmA or control vectors, p35-infected neurons had less active caspase-3 expression, cytosolic cytochrome c and nuclear AIF translocation [4)].

1)

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2)

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3)

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4)

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