

Combination therapy for brain disorders related to BBB dysfunction

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Technology

A combination therapy of approved N-Methyl D- Aspartate receptor (NMDA) receptor blocker and a Transforming Growth Factor beta (TGF- β) receptor antagonist, for treatment of brain diseases associated with blood-brain barrier (BBB) dysfunction. In most common brain disorders, including epilepsy, traumatic brain injury, stroke, and neurodegenerative diseases, the BBB function may be impaired initiating a neural network reorganization, neural dysfunction and degeneration. Despite the clear need for a treatment for these severe physiological conditions, to the best of our knowledge, there is no reported medication for BBB-dysfunction. TGF- β release is a key player that can drive leaky brain vessels to brain damage. Targeting TGF- β receptor can reduce TGF- β release. Prof. Friedman lab had demonstrated the role of the neurotransmitter glutamate in modulating early barrier permeability *in vivo*. Using intravital microscopy, they show that recurrent seizures and the associated excessive glutamate release leads to increased vascular permeability in the rat cerebral cortex, through activation of NMDA receptors. Findings suggest that while NMDA-R activation governs the immediate phase of seizure-induced BBB dysfunction, an independent, non NMDA-R mediated mechanism underlies a slower increase in permeability. The study confirms that combination therapy with existing and FDA-approved drugs such as Memantine hydrochloride (or trade name Ebixa), and Losartan (trade names Ocsaar, Losardex, Losarta, Lotan), which work by blocking NMDA receptors and TGF- β receptors, respectively.

Application

- During the research, the suggested therapy was administered either by i.p. or by loading and implementation of osmotic pumps, or by supplementation to drinking water.
- The route of administration of the pharmaceutical composition depends on the disease or condition to be treated.

Advantages

- Targeting the BBB permeability to protect the CNS - a novel MOA.
- Approved drugs
- Can be relevant for various indications, such as epilepsy, traumatic brain injury, stroke, and NDD
- A combined approach designed to prevent fast and slow mechanisms for BBB dysfunction

Patent

[WO2021/053684A1](#)