Focused ultrasound-mediated blood-brain barrier opening

- Characterization of microbubble cavitation in theranostic ultrasound-mediated blood-brain barrier opening for gene delivery
- The Application of Ultrasound-Induced Blood-Brain Barrier Opening in Neurology and Immunology
- Safe focused ultrasound-mediated blood-brain barrier opening is driven primarily by transient reorganization of tight junctions
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- Ultrasound mediated blood-brain barrier opening increases brain tumor biomarkers: A review of preclinical and clinical trials
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- Characterization of Microbubble Cavitation in Theranostic Ultrasound-mediated Blood-Brain Barrier Opening and Gene Delivery

Focused ultrasound-mediated blood-brain barrier opening is a promising non-invasive technique to deliver therapeutic agents into the brain. The blood-brain barrier is a highly selective semipermeable membrane that separates circulating blood from the brain's extracellular fluid, protecting the brain from potentially harmful substances. However, this barrier also limits the delivery of drugs and therapeutic agents to treat neurological disorders.

Focused ultrasound (FUS) involves using ultrasonic waves that can be precisely targeted and focused on specific brain regions. When applied with microbubbles, small gas-filled bubbles injected into the bloodstream, FUS can transiently disrupt the BBB. This disruption allows therapeutic agents to cross the blood-brain barrier and enter the brain tissue, where they can exert their effects.

Mechanism

Acoustic Cavitation: Microbubbles exposed to ultrasound undergo oscillations or cavitation, causing mechanical stress on the endothelial cells that form the BBB. This stress can lead to the temporary opening of tight junctions between endothelial cells, thereby increasing BBB permeability.

Reversible Opening: The disruption of the BBB induced by FUS is reversible and temporary. Once the ultrasound is turned off and the microbubbles are cleared from the bloodstream, the BBB gradually returns to its normal state.

Precise Targeting: FUS allows for precise targeting of specific brain regions, enabling localized BBB opening without affecting surrounding healthy tissue. This spatial precision minimizes potential side effects and enhances the safety of the procedure.

Real-time Monitoring: Advanced imaging techniques such as magnetic resonance imaging (MRI) can be used to monitor BBB opening in real time during FUS treatment. This monitoring allows for

adjustments to the ultrasound parameters to optimize BBB permeability while ensuring safety.

FUS-mediated BBB opening has shown promising results in preclinical studies for various neurological conditions, including brain tumors, Alzheimer's disease, Parkinson's disease, and stroke. Clinical trials are underway to further evaluate the safety and efficacy of this technique in human patients. If proven successful, FUS could revolutionize the delivery of therapeutics for neurological disorders, potentially offering new treatment options with fewer side effects and improved outcomes.

Indications

Ultrasound enhances drug delivery into the central nervous system (CNS) by opening barriers between the blood and CNS and by triggering release of drugs from carriers. A key challenge in translating setups from in vitro to in vivo settings is achieving equivalent acoustic energy delivery. Multiple devices have now been demonstrated to focus ultrasound to the brain, with concepts emerging to also target the spinal cord. Clinical trials to date have used ultrasound to facilitate the opening of the blood-brain barrier. While most have focused on feasibility and safety considerations, therapeutic benefits are beginning to emerge. To advance translation of these technologies for CNS applications, researchers should standardise exposure protocol and fine-tune ultrasound parameters. Computational modelling should be increasingly used as a core component to develop both in vitro and in vivo setups for delivering accurate and reproducible ultrasound to the CNS. This field holds promise for transformative advancements in the management and pharmacological treatment of complex and challenging CNS disorders [1)].

Focused ultrasound-mediated BBB opening induces cognitive enhancement and neurogenesis; however, the underlying mechanisms have not been elucidated.

Kong et al. investigated the effects of FUS-mediated BBB opening on hippocampal long-term potentiation (LTP) and cognitive function in a 5xFAD mouse model of Alzheimer's disease (AD). We applied FUS with microbubble to the hippocampus and LTP was measured 6 weeks after BBB opening using FUS. Field recordings were made with a concentric bipolar electrode positioned in the CA1 region using an extracellular glass pipette filled with artificial cerebrospinal fluid. Morris water maze and Y-maze was performed to test cognitive function.

The results demonstrated that FUS-mediated BBB opening has a significant impact on increasing LTP at Schaffer collateral - CA1 synapses and rescues cognitive dysfunction and working memory. These effects persisted for up to 7 weeks post-treatment. Also, FUS-mediated BBB opening in the hippocampus increased PKA phosphorylation.

Therefore, it could be a promising treatment for neurodegenerative diseases as it remarkably increases LTP, thereby improving working memory [2)]

Focused ultrasound-mediated blood-brain barrier opening for diffuse midline glioma

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2)
Kong C, Ahn JW, Kim S, Park JY, Na YC, Chang JW, Chung S, Chang WS. Long-lasting restoration of memory function and hippocampal synaptic plasticity by focused ultrasound in Alzheimer's disease. Brain Stimul. 2023 May 19:S1935-861X(23)01781-3. doi: 10.1016/j.brs.2023.05.014. Epub ahead of print. PMID: 37211337.