Microbubble-mediated blood-brain barrier opening

Microbubble-mediated blood-brain barrier (BBB) opening is a technique used in medicine to temporarily and reversibly disrupt the blood-brain barrier, allowing for enhanced drug delivery to the brain. The blood-brain barrier is a protective barrier that separates the bloodstream from the brain and central nervous system, regulating the passage of molecules and preventing many substances, including drugs, from entering the brain. However, in certain medical conditions like brain tumors or neurological disorders, it may be necessary to deliver drugs to the brain.

Here's how microbubble-mediated BBB opening works:

Microbubbles: Microbubbles are tiny gas-filled bubbles, often smaller than red blood cells, that can be injected into the bloodstream. These microbubbles are typically stabilized with a shell made of lipids or proteins.

Ultrasound: High-intensity focused ultrasound (HIFU) or transcranial ultrasound is applied to the specific area of the brain where drug delivery is needed. The ultrasound waves are non-invasive and can penetrate the skull without causing damage to the brain tissue.

Interaction: When the ultrasound waves pass through the microbubbles in the bloodstream, they cause the microbubbles to oscillate or vibrate rapidly. This interaction between ultrasound and microbubbles generates mechanical forces at the microbubble surface.

Blood-Brain Barrier Disruption: The mechanical forces created by the vibrating microbubbles can temporarily disrupt the tight junctions between endothelial cells that make up the blood-brain barrier. This disruption allows small molecules, drugs, and therapeutic agents to pass through the BBB and enter the brain parenchyma.

Drug Delivery: Once the BBB is temporarily opened, drugs that have been administered intravenously can reach the brain in higher concentrations than would be possible without the BBB disruption. This is particularly important for treating brain tumors, neurological diseases, and conditions like Alzheimer's disease.

Reversible: One of the advantages of microbubble-mediated BBB opening is that it is reversible. After the ultrasound is turned off and the microbubbles dissipate from the bloodstream, the blood-brain barrier gradually returns to its normal, impermeable state.

Applications of microbubble-mediated BBB opening include:

Brain Tumor Treatment: It allows for more effective delivery of chemotherapy drugs to brain tumors, improving therapeutic outcomes while reducing systemic side effects.

Neurological Disorders: This technique is being explored for the treatment of neurological disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS).

Research: It is used in preclinical and experimental research to study brain function, develop new therapies, and understand the mechanisms of various brain diseases.

Microbubble-mediated BBB opening is a promising area of research and clinical development, but it

also poses challenges related to safety, precise targeting, and the choice of therapeutic agents. Ongoing research aims to refine and expand the applications of this technique in neurology and oncology.

Focused ultrasound and microbubble-mediated blood-brain barrier opening (FUS-BBBO) is a recent modality used for enhanced drug delivery. It is postulated that coupling FUS with these alternative delivery routes may provide benefits. Multimodality FUS may provide the desired ability to increase the depth of parenchymal delivery following Intrathecal-Intraventricular administration and provide a means for contour directionality with CED, Further the transient enhanced permeability achieved with FUS-BBBO is well established, but drug residence and transit times, important to clinical dose scheduling, have not yet been defined.

An investigation comprises two discrete studies: 1. Conduct a comprehensive quantitative evaluation to elucidate the effect of FUS-BBBO as it relates to varying routes of administration (IT and IV) in its capacity to facilitate drug penetration within the striatum-thalamus region. 2. Investigate the impact of combining FUS-BBBO with CED on drug distribution, with a specific focus on the temporal dynamics of drug retention within the target region.

Firstly, they quantitatively assessed how FUS-BBBO coupled with IT and IV altered fluorescent dye (Dextran 2000kD and 70 kDa) distribution and concentration in a predetermined striatal-thalamic region in naïve mice. Secondly, we analyzed the pharmacokinetic effects of using FUS-mediated BBB disruption coupled with CED by measuring the volume of distribution and time-dependent concentration of the dye.

The results indicate that IV administration coupled with FUS-BBBO successfully enhances delivery of dye into the pre-defined sonication targets. Conversely, measurable dye in the sonication target was consistently less after IT administration. FUS enhances the distribution volume of dye after CED. Furthermore, a shorter time of residence was observed when CED was coupled with FUS-BBBO application when compared to CED alone.

1. Based on the findings, IV delivery coupled with FUS-BBBO is a more efficient means for delivery to deep targets (i.e. striatal-thalamic region) within a predefined spatial conformation compared to IT administration. 2. FUS-BBBO increases the volume of distribution (Vd) of dye after CED administration, but results in a shorter time of residence. Whether this finding is reproducible with other classes of agents (e.g., cytotoxic agents, antibodies, viral particles, cellular therapies) needs to be studied [1)].

1)
Cardenas RU, Laramee M, Dahmane N, Souweidane M, Martin B. Influence of focused ultrasound on locoregional drug delivery to the brain: Potential implications for brain tumor therapy. J Control Release. 2023 Aug 31:S0168-3659(23)00560-6. doi: 10.1016/j.jconrel.2023.08.060. Epub ahead of print. PMID: 37659767.