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HOT TOPICS

Targeted and transient opening of the blood brain barrier in discrete neurocircuits and brain regions

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Delivery of macromolecular therapeutics to the brain faces numerous obstacles, chief of which is transporting them across the blood brain barrier (BBB) of the central nervous system (CNS), in part due to the tight junctions between endothelial cells of the neurovasculature. Despite these difficulties, neuropeptide systems have been continuously noted as promising therapeutic targets. Neuropeptides are often released and diffuse slower than neurotransmitters, and their binding at g-protein coupled receptors have long-lasting effects, making them ideal therapeutic candidates [1, 2]. Yet, the full clinical potential of most neuropeptides remains unrealized as they do not readily translocate across the BBB. Other peptide systems, such as μ-opioid receptor targeting drugs, present the opposite obstacle —they readily diffuse across the BBB, but their ubiquitous actions throughout the brain and periphery lead to off-target issues. Imaging-guided delivery technologies can address these limitations by shuttling therapeutic peptides across the BBB and into specific brain regions, thereby enabling direct access to their therapeutic neuronal target without off-target biodistribution.

Focused ultrasound (fUS) has been proposed as a novel way to increase BBB permeability for a broad range of therapeutic molecules. This technology utilizes ultrasonic transducer arrays to burst dissolved gas bubbles in the blood and mechanically open the BBB endothelium. fUS frequencies are chosen to maximize permeability of specific tissues, while being mindful of constraints of tissue heating, acoustic distortion by skull bones and power limitations [3]. The accessibility of fUS to assist with trans-BBB drug delivery has risen as advancements in wireless power transfer coupled with microscale implants allow for millimeter precision of US targeting [4]. Contrast-agent-assisted fUS utilizes microbubbles that can be ruptured at low US intensities to significantly reduce the acoustic pressures required for BBB permeabilization. Nanoemulsion contrast agents go one step further as, due to their small size, they can diffuse within the tight junctional space to allow more tunable and precise BBB opening under fUS, thereby improving delivery efficiencies and minimizing brain damage relative to microbubbles (Fig. 1). The potential of these nanoscale platforms to enable US-guided delivery of biomacromolecules at the periphery has already been demonstrated [5, 6]. In addition to fUS as a delivery trigger, nanoemulsions can be engineered to respond to thermal, optical, and magnetic stimuli as well—highlighting the versatility of this technology for drug delivery to the CNS and other hard-to-access tissues.

Pairing nanoscale contrast agents with fUS is poised to open new opportunities in brain-region-specific drug delivery, offering extreme precision and minimally invasive administration. Combining these technologies provides an advancement in (1) preferentially localizing compounds to not only the CNS, but specific circuits and regions within the brain, without off-target effects, and (2) more efficient, controlled, and safer BBB permeabilization. This will allow for delivery of therapeutic compounds (peptides, antibodies, gene therapies, and other cargo, for both treating and

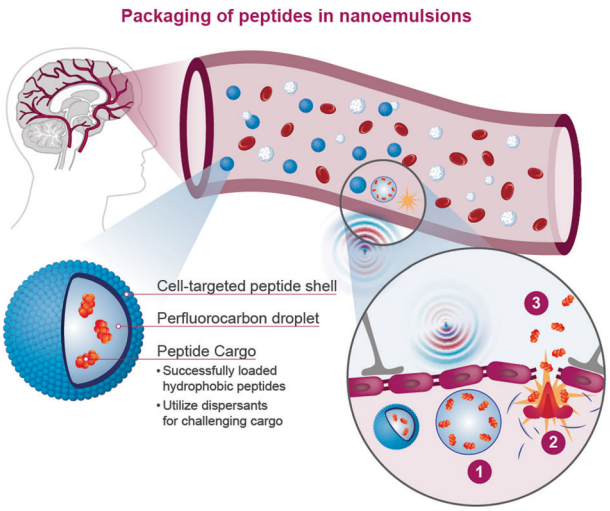

Fig. 1 Representative model for how focused ultrasound can be combined with nanoemulsions for precision drug delivery to the brain. Peptides, antibodies, or other molecules of interest are packaged within nanoemulsion droplets that can be vaporized under ultrasound stimulation. When combined with focused ultrasound modalities for site-specific activation, this platform has the potential for BBB opening and drug delivery with extreme precision. Ongoing clinical trials will need to bridge safety and efficacy concerns, and it will be vital to make the technology medically accessible outside of the operating room. Some uses of this technology, included imaging-guided drug delivery, may always necessitate clinic access. Inset, (1) ultrasound stimulation of the brain allows for both cavitation of the emulsion and release of the cargo (2), and (3) permeabilization of the BBB.

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preventing disease) within targeted neurocircuits and localized regions. Leveraging the low-cost, transportable and biocompatible nature of US will additionally avoid restricting these imaging-guided trans-BBB delivery modalities to the operating room and broaden their therapeutic impact in various clinical and non-clinical settings.

REFERENCES

1. Brockway DF, Crowley NA. Turning the 'tides on neuropsychiatric diseases: the role of peptides in the prefrontal cortex. Front Behav Neurosci. 2020;14. https://doi.org/10.3389/fnbeh.2020.588400
2. Dao NC, Brockway DF, Crowley NA. In vitro optogenetic characterization of neuropeptide release from prefrontal cortical somatostatin neurons. Neuroscience. 2019;419:1–4. https://doi.org/10.1016/j.neuroscience.2019.08.014
3. McMahon D, Poon C, Hynynen K. Evaluating the safety profile of focused ultrasound and microbubble-mediated treatments to increase blood-brain barrier permeability. Expert Opin Drug Deliv. 2019;16:129 https://doi.org/10.1080/17425247.2019.1567490
4. Kashani Z, Ilham SJJ, Kiani M. Design and optimization of ultrasonic links with phased arrays for wireless power transmission to biomedical implants. IEEE Trans Biomed Circuits Syst. 2022;16. https://doi.org/10.1109/TBCAS.2022.3140591
5. Sloand JN, Nguyen TT, Zinck SA, Cook EC, Zimudzi TJ, Showalter SA, et al. Ultrasound-guided cytosolic protein delivery via transient fluorous masks. ACS Nano. 2020;14:4061–73. https://doi.org/10.1021/ACSNANO.9B08745
6. Sloand JN, Rokni E, Watson CT, Miller MA, Manning KB, Simon JC, et al. Ultrasound-responsive nanopeptisomes enable synchronous spatial imaging and inhibition of clot growth in deep vein thrombosis. Adv Health Mater. 2021;10:2100520. https://doi.org/10.1002/ADHM.202100520

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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