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

Nicole A. Crowley[1,2,3*] and Scott H. Medina[2,3*]

1 Department of Biology, Penn State University, University Park PA 16802

2 Department of Biomedical Engineering, Penn State University, University Park PA 16802

3 The Huck Institutes of the Life Sciences, Penn State University, University Park PA 16802

*Correspondence to:
Nicole A. Crowley, Ph.D.
Assistant Professor
Departments of Biology
And Biomedical Engineering
Penn State University
326 Mueller Lab
University Park, PA 16802
Tel: (814) 863 – 0278
E-Mail: nzc27@psu.edu

Scott H. Medina, Ph.D.
Associate Professor
Department of Biomedical Engineering
Penn State University
511 CBE Building
University Park, PA 16802
Tel: (814) 863 – 4758
E-Mail: shm126@psu.edu

Abbreviated title: *targeted BBB drug delivery*

NPPR Hot Topics
Total words: 600
Total figures: 1
Total references: 6

Main

Delivery of macromolecular therapeutics to the brain faces numerous obstacles, chief of which is transporting them across the stringent blood brain barrier (BBB) of the central nervous system (CNS). This is in part due to the tight junctions between endothelial cells of the neurovasculature, which forms a strict interface that prevents most circulating substances from entering the brain. Despite these difficulties, neuropeptides and their receptors, which are distinct from classical neurotransmitters, have been continuously noted as promising therapeutic targets in the preclinical literature, which relies on invasive routes of administration (e.g. in-dwelling cannulas targeted at specific brain regions) to overcome the BBB. Neuropeptides are often released and diffuse slower than neurotransmitters, and their binding at g-protein coupled receptors (GPCRs) has longer lasting effects than neurotransmitter binding at ionotropic receptors, making them ideal therapeutic candidates (Brockway & Crowley, 2020; Dao et al., 2019). Yet, the full clinical potential of most neuropeptides remains unrealized as these preclinical methods of administration are untenable for clinical purposes. 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 both of 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 (McMahon et al., 2019). 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 (Kashani et al., 2022). However, unassisted fUS requires high acoustic intensities to be operational and thus can lead to unintentional neuronal damage. 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. The potential of these nano-scale platforms to enable US-guided delivery of biomacromolecules at the periphery has already been demonstrated (Sloand et al., 2020, 2021). 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 nano-scale contrast agents with fUS is poised to open new opportunities in brain-region specific drug delivery, offering both extreme precision and minimally-invasive administration. With respect to treating brain disorders using neuropeptides, combining these technologies provides an advancement in (1) preferentially localizing peptidic compounds to not only the CNS, but specific circuits and regions within the brain, without off-target binding to receptors elsewhere in the body, and (2) more efficient, controlled and safer BBB permeabilization. This will allow for delivery of therapeutic compounds (both peptides and others) within targeted neurocircuits. 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.

ACKNOWLEDGEMENTS

We thank members of the Crowley and Medina labs for helpful discussions related to this topic.

AUTHOR CONTRIBUTIONS

NAC and SHM jointly conceived the topic for this commentary based on shared funding. NAC and SEM contributed equally to manuscript preparation.

FUNDING INFORMATION

NAC is supported by NIH grants R01AA029403-01A1, R21AA028088-01, and P50AA017823. SHM is supported by NIH grants R21DK128638-01A1, R35GM142902-01 and NSF grant DMR-1845053. NAC and SHM are jointly supported by the Benkovic Research Initiative.

COMPETING INTERESTS

This commentary was prepared in the absence of any personal, professional, or financial relationships considered a conflict of interest.

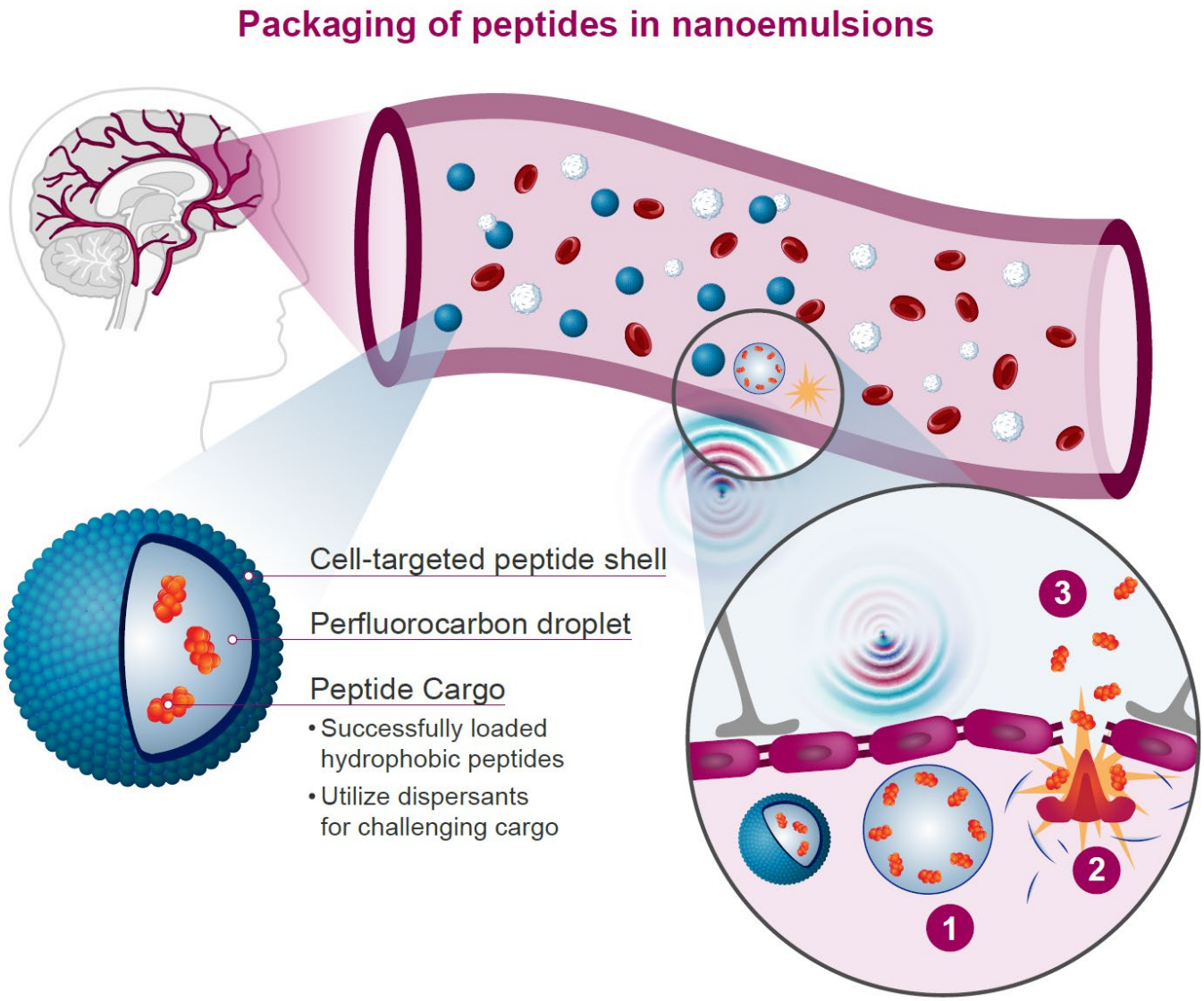

Figure 1

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 can be packaged in droplets which collapse under ultrasound stimulation. When combined with targeted ultrasound stimulation for site-specific cavitation of the nanoemulsion and opening of the BBB, this technological advancement has the potential for therapeutic drug targeting with extreme precision. *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.*

References

Brockway, D. F., & Crowley, N. A. (2020). Turning the 'Tides on Neuropsychiatric Diseases: The Role of Peptides in the Prefrontal Cortex. *Frontiers in Behavioral Neuroscience*, *14*. https://doi.org/10.3389/fnbeh.2020.588400

Dao, N. C., Brockway, D. F., & Crowley, N. A. (2019). In Vitro Optogenetic Characterization of Neuropeptide Release from Prefrontal Cortical Somatostatin Neurons. *Neuroscience*, *419*, 1–4. https://doi.org/10.1016/j.neuroscience.2019.08.014

Kashani, Z., Ilham, S. J. J., & Kiani, M. (2022). Design and Optimization of Ultrasonic Links With Phased Arrays for Wireless Power Transmission to Biomedical Implants. *IEEE Transactions on Biomedical Circuits and Systems*, *16*(1). https://doi.org/10.1109/TBCAS.2022.3140591

McMahon, D., Poon, C., & Hynynen, K. (2019). Evaluating the safety profile of focused ultrasound and microbubble-mediated treatments to increase blood-brain barrier permeability. *Expert Opinion on Drug Delivery*, *16*(2), 129. https://doi.org/10.1080/17425247.2019.1567490

Sloand, J. N., Nguyen, T. T., Zinck, S. A., Cook, E. C., Zimudzi, T. J., Showalter, S. A., Glick, A. B., Simon, J. C., & Medina, S. H. (2020). Ultrasound-Guided Cytosolic Protein Delivery via Transient Fluorous Masks. *ACS Nano*, *14*(4), 4061–4073. https://doi.org/10.1021/ACSNANO.9B08745

Sloand, J. N., Rokni, E., Watson, C. T., Miller, M. A., Manning, K. B., Simon, J. C., & Medina, S. H. (2021). Ultrasound-Responsive Nanopeptisomes Enable Synchronous Spatial Imaging and Inhibition of Clot Growth in Deep Vein Thrombosis. *Advanced Healthcare Materials*, *10*(16), 2100520. https://doi.org/10.1002/ADHM.202100520