Enhanced Delivery and Imaging of Neurotherapeutics via US, MRI, SPECT

Michael Valdez[1], Eriko Yoshimaru[1], Pier Ingram[2], John Totenhagen[1], Aaron Forbes[3], Stephen K. Moore[1], Paul Helquist[4], Terry O. Matsunaga[5], Russell Witte[1], Lars R. Furenlid[6], Zhonglin Liu[2], Robert P. Erickson[7], and Theodore Trouard[1]

[1]Biomedical Engineering, University of Arizona, Tucson, Arizona, United States, [2]Radiology, University of Arizona, Tucson, Arizona, United States, [3]Chemistry & Biochemistry, University of Notre Dame, South Bend, North Carolina, United States, [4]Chemistry & Biochemistry, University of Notre Dame, Notre Dame, IN, United States, [5]Radiology, University of Arizona, Tuscon, Arizona, United States, [6]Radiology and Optical Sciences, University of Arizona, Tucson, Arizona, United States, [7]Pediatrics, University of Arizona, Tucson, Arizona, United States

Introduction

Treatment of neurological disorders is hampered by the inability of drugs to get across the blood-brain barrier (BBB). Over the last several years, novel techniques that use focused ultrasound (FUS) energy in combination with microbubble (μB) contrast agents have been developed that reversibly open up the BBB [1]. Foundational studies have been carried out in several animal models, including mice [2]. BBB opening is readily verified with MRI using gadolinium contrast agents. This does not give specific information about the delivery of actual drugs to the brain. To address this point, we have initiated studies combining FUS-mediated BBB opening with high-resolution single photon computed tomography (SPECT) of radiolabeled ^{123}I-tyr-beta-cyclodextrin (^{123}I-tyr-BCD) in mice. BCD is a promising treatment for Niemann-Pick type C (NPC) disease, a childhood affliction that involves errors in cholesterol trafficking and results in neurodegeneration and death in the early teen years. BCD has shown promising results in animal models of NPC disease when delivered directly into the brain.

Methods

Mice were imaged prior to BBB opening in a 7T Bruker Biospec MRI system. A 72 mm ID birdcage coil was used for excitation and a 4-channel phased array coil was used for reception. The mice were secured in an MRI cradle with ear bars and a bite bar. Rapid whole-brain 3D T1-weighted GRE images (5 minute acquisition) were obtained prior to and after IP injection of Gd-DTPA. BBB opening utilized a 40 μL bolus of custom gas filled μBs that were injected into the tail vein, followed by a 120 μL saline flush. Immediately after the injection, 3.3 MHz FUS was transcranially administered to the mouse brain. Thirty 2-second sonications were delivered with a 5 second pause between sonications (37% duty cycle, 6 ms pulse width, 0.80 MPa peak negative pressure). A custom built positioning apparatus (Fig. 1) was used to position the FUS transducer (30 mm diameter, 49.4 mm focal length) such that its focal spot was within the brain of the mouse. After FUS, the mice were returned to their original position in the MRI magnet and identical T1-weighted imaging was carried out for 30 minutes. T1-weighted 2D spin-echo images were also obtained. Other mice underwent the same procedure, except that no FUS was applied. Mice were allowed to recover and showed no obvious deficits in neurologic function. Within 3 hours of the MRI procedure, pairs of mice were injected with ^{123}I-tyr-BCD and imaged simultaneously using a custom-built γ-ray scintigraphy system to verify the injection of ^{123}I-tyr-BCD. Following this, mice were individually imaged on a custom built SPECT/CT imaging system, FaCT [3] to determine the distribution of ^{123}I-tyr-BCD in the brain. Finally, mice were sacrificed and excise brain slices underwent autoradiography to verify in vivo measurements.

Results and Discussion

MRI image enhancement maps after the administration of Gd-DTPA, μBs and FUS are shown in Fig. 2. There is a strong increase in signal in the brain parenchyma in the mouse after receiving FUS and the diffusion of Gd-DTPA through the tissue is apparent 90 minutes post FUS. γ-ray scintigraphy images of the two mice are shown in Fig. 3. Greater signal intensity is seen in the brain region of the animal that received FUS compared to the control animal. SPECT images are shown in Fig. 4 where increased signal in the brain of the experimental mouse is observed. This increase was confirmed by a 4.8 times increase in signal in autoradiographic images of brain slices (Fig. 5). This demonstrates the focal BBB opening procedures allow passage of ^{123}I-tyr-BCD into the brains of mice. While these experiments are directed towards NPC disease, they could have a significant impact on other common neurological disorders (e.g. Alzheimer's and Parkinson's).

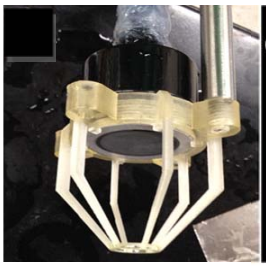

Fig. 1. *Apparatus for coupling FUS transducer beam to mouse head when mouse is attached to the cradle.*

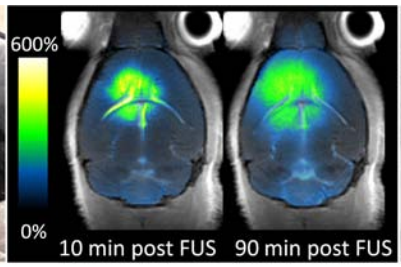

Fig. 2. *T1-weighted MRI enhancement maps (percent signal increase). Signal increase from IP injection of Gd-DTPA (w/Gd). 10 and 90 minutes post FUS and 40 μL solution of μB. Enhancement shows open BBB and diffusion of Gd-DTPA over time.*

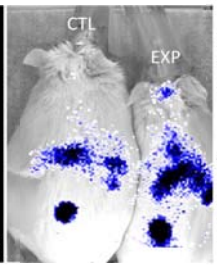

Fig. 3. *Planar scintigraphy imaging of. Experimental mouse (EXP) received FUS+μB and shows from ^{123}I-tyr-BCD signal in brain. The control did not receive FUS.*

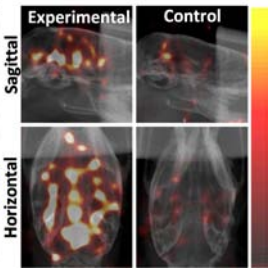

Fig. 4. *Mice in Fig. C imaged with FaCT system showing signal from ^{123}I-tyr-BCD. Two different orientations show greater signal in experimental than control.*

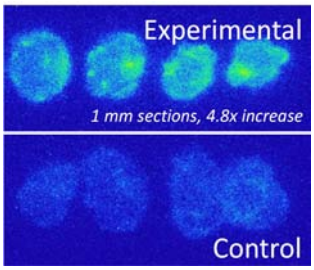

Fig. 5. *Autoradiography of the brains of the mice used in Fig. D. Four 1mm slices from each mouse show a 4.8x increase in signal from ^{123}I-tyr-BCD.*

References

[1] Hynynen et al. J Neurosurg. 105(3):445-54. (2006)
[2] McDannold et al. Radiology. al. Ultrasound Med Biol. 36(9):1445-1459. (2012)
[3] Moore, Furenlid, Barrett. IEEE NSS. 5585-5587. (2008)