Focused Ultrasound Interventions Increase Neurogenesis and Reduce Anxiety in Wild-Type Mice

Background, Motivation and Objective

Focused ultrasound in conjunction with microbubbles can noninvasively and transiently open the BBB (FUS-BBBO) as a result of exerting mechanical effects on the vasculature. Recently, focused ultrasound without microbubbles (FUS-N) has been shown to enhance memory in Alzheimer's mice. A comprehensive understanding of the mechanisms inducing the observed cognitive benefits is thus warranted. Hippocampal neurogenesis has been shown to play a critical role in memory formation and anxiety-like behavior. This study interrogated both FUS-N and FUS-BBBO and assessed their effects on hippocampal neurogenesis and anxiety in wildtype mice.

Statement of Contribution/Methods

Female, 9-week-old B6129SF2/J mice (n=5/group) underwent anesthesia sham, FUS-BBBO, or FUS-N. Sonications were targeted to the bilateral hippocampus. FUS-BBBO used a single-element FUS transducer (f_c = 1.5 MHz, PNP: 0.45 MPa, Imasonic) and was co-administered with intravenously injected in-house microbubbles ($8x10^8$ MB/mL). FUS-N took place using a single-element FUS transducer (H204, f_c = 1.68 MHz, PNP: 4 MPa, Sonic Concepts). Three weeks after treatment, all groups underwent the Open Field Test (OFT) followed by assessment of neurogenesis through doublecortin (DCX) immunohistochemistry (Santa Crux Biotechnology, sc-8066). DCX+ neuronal cells in the dentate gyrus subventricular zone of the hippocampus were quantified through ImageJ.

Results/Discussion

Time elapsed in the center zone of the OFT box increased for both FUS interventions indicating equivocal reduced anxiety in both FUS groups (Figure A). Anxiety was significantly reduced among the FUS-N mice compared to the sham group (P = 0.04). The relationship between the number of DCX+ cells and Time in the Center Zone (s) was directly proportional in both FUS-N (R^2 = 0.39, P = 0.05) and FUS-BBBO (R^2 = 0.69, P = 0.006) treated cohorts with FUS-BBBO inducing slightly more enhanced and significant neurogenesis compared to FUS-N (Figure B). The findings strongly indicate that increased hippocampal neurogenesis is accomplished with both FUS-N and FUS-BBBO and it is correlated with improved behavioral outcomes such as reduced anxiety in wildtype mice. Ongoing studies are assessing similar effects in Alzheimer's mice.