Focused Ultrasound Mediated Effect on the Blood - Cerebrospinal Fluid Barrier and its impact in reduction of Alzheimer's pathology

Background, Motivation and Objective

Focused ultrasound (FUS) - mediated blood - brain barrier (BBB) opening has been shown to transiently, noninvasively, and safely open the BBB. Efficacy and safety studies indicate FUS - BBBO reduces Alzheimer's Disease (AD) pathological proteins, including amyloid - β (Aβ) peptides, a synaptic by-product . In the homeostatic brain, Aβ is cleared through active transport across the BBB and blood - cerebrospinal fluid barrier (BCSFB), a barrier formed by the tight junctions between choroid plexus (CP) epithelial cells primarily via, lipoprotein receptor - related protein -1 (LRP1), a marker shown to increase in expression as a result of AD promoted choroid plexus dysfunction. This removal process is impaired in the case of AD. This study aims to evaluate the FUS-mediated opening of the BCSFB (BCSFBO) and its role in reducing Aβ and LRP1.

Statement of Contribution/Methods

Seven 1-year old female 3xTg AD mice were divided into FUS - BCSFBO (n = 3) and sham groups (n =4). FUS - BCSFBO mice underwent a bilateral sonication of the hippocampus with a single - element, spherical segment FUS transducer (fc = 1.5 MHz, focal depth: 60 mm, radius: 30 mm, Imasonic, PNP: 450 kPa, PRF: 10, PL: 6.7 ms) in combination with a 1:10 dilution of in house made lipid-coated, perfluorobutane polydisperse microbubbles in saline (mean diameter:1.4 µm). After sacrifice 5 days post - treatment with saline perfusion, brains were fixed in 4% paraformaldehyde and 30% sucrose and cryosectioned to 35 µm coronal sections on a cryostat (Leica). Sections were stained for LRP1 and Aβ($Methoxy - X04$) . 10x images of the lateral ventricle and 20x images of the choroid plexus were acquired using an Olympus BX61 Microscope and image analysis was performed using ImageJ (NIH).

Results/Discussion

FUS - BCSFBO treated mice have less Aβ as compared with sham mice in the lateral ventricle, consistent (Fig.1b). Fluorescence intensity for each group was quantified and agrees with qualitative analysis (Fig.1c). Reduced expression of Aβ and LRP1 was detected (Fig. 1b) and quantified (Fig. 1c) in the choroid plexus for the experimental group with significance shown in LRP1 (p-value = 0.0023). The reduction of AD pathology (Aβ) and LRP1 is indicative of improved receptor function. The findings presented demonstrate transport through the BCSFBO as a pathway through which reduction of AD pathology is facilitated.