Natural aging and Alzheimer's disease pathology increase blood-brain barrier opening volume and prolong BBB closing timeline without affecting closing rate

Rebecca Noel[1], Robin Ji[1], Alec J. Batts[1], Alina Kline-Schoder[1] and Elisa Konofagou[1,2]
[1]Department of Biomedical Engineering, [2]Department of Radiology, Columbia University, New York, NY, USA

Introduction

Focused Ultrasound (FUS) paired with systemically administered microbubbles (MBs) transiently opens the blood-brain barrier (BBB), locally activating neuronal cell types and enabling the passage of large molecules to which the in-tact barrier is otherwise impermeable. The safety of FUS+MB has been well established as a technique for local and transient BBB opening. However, several factors influence the brain's response to BBB opening, necessitating a study to clarify the individual effects of age and neuropathology, such as amyloid plaque and tau tangles in Alzheimer's disease (AD), on the extent of BBB opening and the timeline for reinstatement of the BBB, or BBB closing.

Methods

Four groups of male mice spanning two different age groups (1 and 2 years old) and two genotypes (WT and 3xTg) were treated with FUS+MB bilaterally targeting the hippocampus (n = 4-5 per group). The 3xTg mouse line serves as a model of AD, recapitulating both human amyloid and tau pathology. The animals were sonicated at a pressure of 450 kPa for 60 seconds at each target. Throughout the application of FUS and MB the total cavitation dose was quantified for each subject. Immediately following FUS treatment each subject was administered an intraperitoneal injection of Gadolinium (Gd) contrast agent, and the BBB opening volume was visualized using contrast-enhanced T1-weighted MRI. The mice underwent the same MRI protocol every 24 hours until their BBB closed completely. The opening volumes for each subject on each day were then quantified from the MRIs in Matlab, and linear regressions and F tests were performed in Graphpad PRISM.

Results & Discussion

Figure 1A shows axial T1-weighed MRI images acquired 1 and 120 hours post-FUS when the BBB is open and closed respectively. Figure 1B depicts the BBB opening volume resulting in each group of mice normalized by the cavitation dose they received in dB. Although not significant by one-way ANOVA with multiple comparisons, the trend toward larger BBB opening response to cavitation in aged and transgenic mice is clear and supported by subsequent data. Figure 1 C-D demonstrates the effect of AD pathology, while Figure 1 E-F depicts the effect of age on opening volume and closing time. F-test analysis of the linear regression models reveals a statistically significant difference in y-intercept between WT and 3xTg mice at one year of age ($p<0.001$, Fig. 1C) and between 1- and 2-year-old WT mice ($p<0.001$, Fig. 1E). The slopes of the linear regression models do not vary significantly, indicating that BBB closing occurs at a similar rate regardless of age or genotype. However, the prolonged closing timeline and statistically significant difference between y-intercepts in mice progressed in age (Figure 1E) or AD pathology (Figure 1C) indicates that both advanced age (in WT mice) and the presence of AD pathology may increase the brain's susceptibility to BBB opening by FUS+MB, causing larger openings and prolonged closing timelines, without affecting the rate of closing. Understanding the influence of age and pathology on BBB opening and closing may shed light on the biological mechanisms that underlie these processes and inform clinical studies in populations most susceptible to neurodegenerative disease.

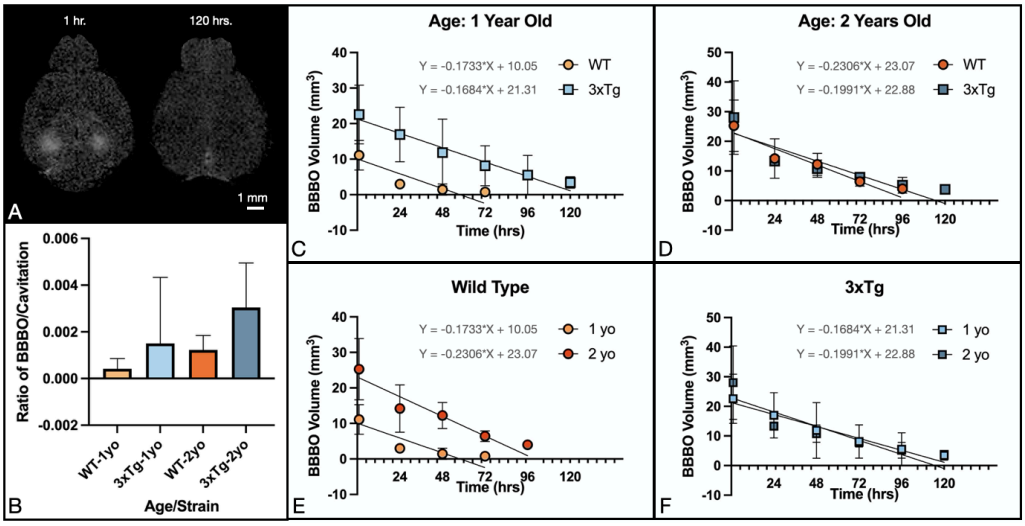

Figure 1: BBB opening volume as a function of time. (A) T1-weighted axial MRI scans depicting the open and in-tact BBB at 1 and 120 hours. (B) BBB opening 1 hour post-FUS normalized by cavitation dose. Not significant by one-way ANOVA with multiple comparisons. (C) Average BBB opening volume over time with linear regression in 1-year-old WT ($R^2 = 0.61$) and 3xTg ($R^2 = 0.48$) mice. Y intercepts significantly different by F test ($p<0.001$) (D) Average BBB opening volume over time with linear regression in 2-year-old WT ($R^2 = 0.62$) and 3xTg ($R^2 = 0.58$) mice. (E) Average BBB opening volume over time with linear regression in WT 1-year-old ($R^2 = 0.61$) and 2-year-old ($R^2 = 0.62$) mice. Y intercepts significantly different by F test ($p<0.001$) (F) Average BBB opening volume over time with linear regression in 3xTg 1-year-old ($R^2 = 0.48$) and 2-year-old ($R^2 = 0.58$) mice.