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Determining a Cavitation Threshold for Focused Ultrasound Enhanced Intranasal Drug Delivery

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Background, Motivation and Objective

Focused ultrasound enhanced intranasal drug delivery (IN+FUS) is a unique noninvasive approach that utilizes the olfactory pathway to administer drugs directly to the brain. Our group has shown that IN+FUS provides a more homogenous distribution of molecules in the targeted region than intranasal delivery alone. The underlying mechanism of IN+FUS is believed to be due to the microbubble pump effect, where microbubble cavitation causes expansion and contraction of the perivascular space. Therefore, the aim of this study is to investigate a potential cavitation threshold that is required for successful IN+FUS.

Statement of Contribution/Methods

Intranasal (IN) delivery of 3kDa dextran was administered to wild-type mice (n = 10) as 3μL droplets to alternating nostril, for a total of 48μL. Afterwards, the left caudate putamen was sonicated for 1 minute with a single element FUS transducer (center frequency: 1.5MHz, peak negative pressure: 450kPa or 650kPa, pulse repetition frequency: 5Hz), with the contralateral side used as the control case. A pulse-echo transducer confocally aligned with the FUS transducer was used for passive cavitation detection (PCD) to monitor the cavitation in the targeted region. Frequency analysis of the cavitation was quantified by integration of harmonic and ultraharmonic peaks for the first 50 pulses, yielding a summated cavitation dose (CD). T1-weighted MR contrast imaging was performed to confirm FUS targeting and fluorescence microscopy was used to quantify dextran distribution.

Results/Discussion

Our results show that there is a CD threshold that can be used to predict success of IN+FUS. Sufficient IN+FUS was characterized by diffuse distribution of fluorescence in the targeted region compared to the contralateral side (Figure 1). A CD above 11 V·s is necessary for successful dextran delivery as evidenced by an increased fluorescence homogeneity in the caudate putamen compared to the contralateral side. It is important to note that these results only apply when IN delivery was successful. IN delivery alone generates a sparse distribution of dextran throughout the brain, while applying FUS after IN further enhances the diffusivity of the dextran across the targeted region. As a result, these findings indicate that there exists a minimum cavitation response required for the microbubble pump effect to enhance IN delivery.

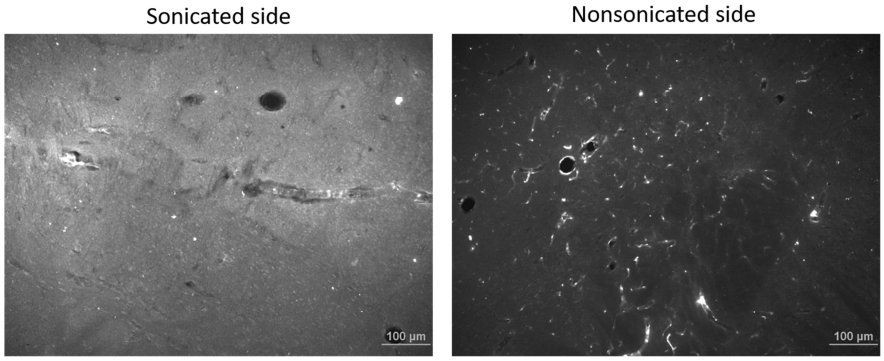

Figure 1: Horizontal sections of successful FUS+IN, comparing the sonicated caudate putamen and the contralateral nonsonicated side. Homogenous diffusion of dextran throughout the structure can be seen in the sonicated side, compared to the more heterogeneous distribution on the nonsincated side, where the dextran is trapped within the perivascular space. Images are shown at 10x magnification.