MRI-guided focused ultrasound for local delivery of anti-Aβ antibodies in a mouse model of Alzheimer's disease

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Purpose

Alzheimer's disease (AD) is characterized by neuronal loss, paired helical filaments and senile plaques composed of amyloid-beta peptides (Aβ). Due to evidence that Aβ is neurotoxic[1], many recent AD treatments focus on targeting Aβ, in an attempt to clear Aβ loads and halt brain degeneration. A subset of these therapies includes passive immunization, which involves the use of intravenously administered anti-Aβ antibodies that circulate in the bloodstream and draw Aβ out of the brain. An important limitation to the success of immunotherapy in AD is that most systemic antibodies will not cross the blood-brain barrier (BBB). To circumvent this problem, previous studies have shown that the use of focused ultrasound (FUS), in the presence of a microbubble ultrasound contrast agent, can cause localized and transient permeability of the BBB[2], allowing agents as large as antibodies into the brain. MRI guidance can also be used to accurately position target regions and confirm BBB opening following FUS.

Direct delivery of anti-Aβ antibodies to the brain has the potential advantages of lowering antibody dosages required for efficacy as well as lowering the concentration of antibodies left in the bloodstream that may elicit detrimental side effects. We propose that MRIgFUS treatment can be used, with lower doses of anti-Aβ antibodies, to target Aβ in the brain of the TgCRND8 mouse model of AD and reduce Aβ loads in targeted cortical areas. In this study, we evaluate the spatio-temporal distribution of anti-Aβ antibodies in the brain after MRIgFUS treatments and the subsequent effect of this treatment on Aβ pathology within 4 days post-treatment.

Methods

TgCRND8 mice (n=6, age: 4 months) received tail vein injections of the anti-Aβ antibody BAM-10, gadolinium and *Definity* microbubbles. MRIgFUS was applied in a line along the right hemisphere. At different time-points post-treatment, TgCRND8 mice were sacrificed and their brains processed for biochemical analyses and quantitative imaging, including design-based stereology to estimate the number and size of Aβ plaques in the cortex.

Results

We confirmed that transcranial MRIgFUS delivered anti-Aβ antibodies from the bloodstream to targeted regions of the brain, which corresponded to regions of BBB opening from MRI post-treatment scans. BAM-10 antibodies entered the brain *in vivo* where they co-localized with other anti-Aβ antibodies applied *ex vivo*, on the right hemisphere of the brain. Within days, MRIgFUS-delivered anti-Aβ antibody significantly reduced both Aβ plaque number and size by 12% (*p=0.008, *p=0.048), in the cortical regions targeted.

Conclusions

Transcranial MRIgFUS locally and efficiently delivers antibodies to targeted cortical areas of the brain, resulting in a rapid reduction in Aβ pathology by 4 days post-treatment. Thus, MRIgFUS shows promise as a therapeutic strategy for delivery of anti-Aβ agents to the brain for treatment of Alzheimer's disease, and by extension, other neurodegenerative diseases.
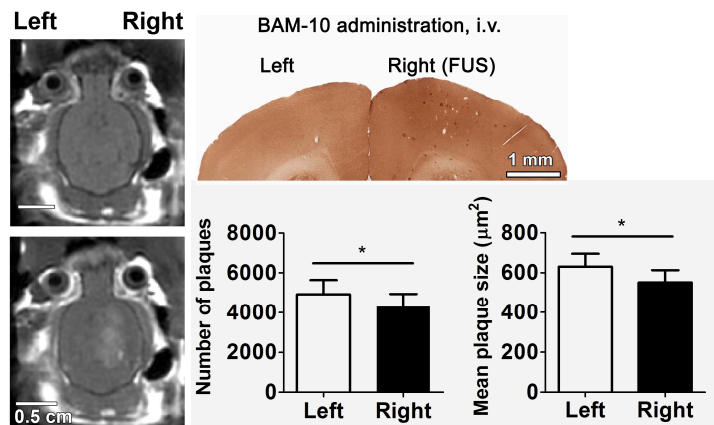

Figure 1. MRIgFUS locally delivers anti-Aβ antibodies to targeted regions of the brain and reduces Aβ plaque burden in TgCRND8 mice. MRI imaging is used prior to FUS (Left, top) to position FUS foci and following FUS (Left, bottom) to confirm BBB opening. Antibody is detected only on the right side of the brain following MRIgFUS delivery (Right, top). This treatment led to a significant reduction in Aβ plaque number and size (Right, bottom).

References:
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2. Hynynen K, *et al*. (2001). Radiol. **220**: 640-646.