Using ultrasound for enhanced drug delivery in Alzheimer’s disease

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Methods

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Results

FUS resulted in the opening of the iBEC monolayer both in AD and control cells (Ctrl-iBEC) identified by loss of cell-cell connections (Fig 3A). Cell monolayer fully recovered 24h following treatment (Fig. 3A).

Permeability to fluorescently-conjugated dextran and amyloid-β was significantly increased 24h following FUS treatment in AD-iBECs, compared to untreated (UT) cells and Ctrl-iBECs (Fig. 3B).

Conclusions

Our preliminary experiments using antibodies designed to treat AD have identified increased antibody delivery through the BBB model following FUS (Fig. 4).

Purpose

The blood-brain barrier (BBB) surrounds brain microvessels (Fig. 1A). It protects the brain, but simultaneously challenges drug delivery. Focused ultrasound (FUS) is a novel technique to transiently open the BBB for increased drug delivery (Fig. 1B). We investigated the ability to model FUS-mediated BBB opening in vitro in an Alzheimer’s disease (AD) patient cell model.

Figure 1. A) An illustration of the brain vasculature where the BBB is formed. B) A schematic of FUS-mediated BBB opening and subsequent drug delivery. Created using Biorender.com.

Figure 2. A) Workflow of AD-iBEC generation. Created using Biorender.com. B) Immunofluorescence of BBB markers occludin and claudin-5 in iPSC-derived iBECs.

Figure 3. A) iBEC monolayer immediately (0h) and 24h following FUS. B) Dextran and amyloid-beta permeability in untreated (UT) and FUS-treated Ctrl- and AD-iBECs cells. Adapted from Oikari et al. 2020 Stem Cell Reports.

Figure 4. A) Schematic of in vitro antibody delivery through the iBEC monolayer using FUS. Created using Biorender.com. B) Permeability of anti-amyloid-beta antibody (Aducanumab) is increased in iBECs following FUS.

Our data demonstrates the ability to model FUS-mediated BBB opening in vitro using patient-derived cells. We also demonstrate differences in FUS response between AD and control cells, highlighting disease-specific differences. Our BBB cell model provides a basis for an in vitro platform to screen for ultrasound-deliverable drugs in AD.

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