Curing Alzheimer's: Use of microbubbles and ultrasound to increase blood brain barrier permeability for drug delivery

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Abstract

Alzheimer's disease is a neurodegenerative disorder that is estimated to affect over 6 million Americans. The disease is marked by the presence of plaques and tangles in the brain. While some trials have hoped to combat these plaques using antibodies, the semipermeable blood brain barrier (BBB) blocks their passage. In order to get antibodies across the BBB, we utilized sonication and ultrasound to assist in this process. To test, we used transwell membranes as the BBB, Dextran as antibodies, and substitute sonication and ultrasound devices. We tested the difference between a lipid solution and distilled water to support microbubbles, the difference between ultrasound exposure and none, and the difference between solicitation and none. We found that the combination of sonication and ultrasound considerably increased the ability for the Dextran to pass through the membrane. This methodology of combining ultrasound and sonication to help cross the BBB is significant as many treatments fail because the BBB blocks its passage. While this can be applied to Alzheimer's treatment to get antibodies to the brain, it can also be applied to other treatments that require passage across the BBB.

Introduction

- ➢Research on Alzheimer's began in the early 1970.
- ➢Neurodegenerative disorder that affects cognitive and muscular function.
- ➢Impacts one in nine older than 65 years of age and one in three older than 85 years of age (1).
- ➢Presentation of plaques and tangles in their brain.
- ➢What is not known about this disease are ways to treat it.
- ➢Treatment is difficult because drugs cannot pass through the blood brain barrier (BBB; Figure 1)
  - ○BBB is a semipermeable membrane that restricts what can pass from the blood into the brain
- ➢We propose that by using amyloid-beta antibodies along with microbubbles and ultrasound (to administer the antibodies) we can destroy plaques and tangles.

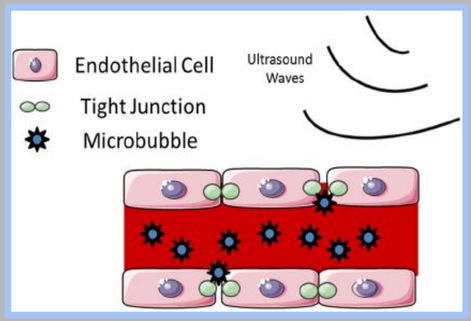
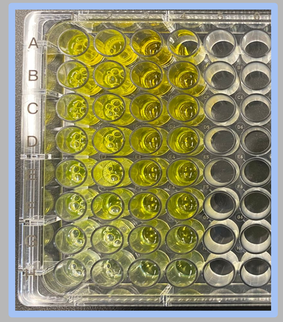


Figure 1 (left): Blood brain barrier exposed to ultrasound and microbubbles

Figure 2 (right): Serial dilution for standard curves. Left two columns experimental, right two control



Methods

Experimental Details

- ➢ *Dextran*: fluorescent polysaccharide; model for antibody.
- ➢ *Transwell membrane inserts*: membranes through which molecules of 0.8 um can pass (Model BBB; Figure 3).
- ➢ *Sonication*: performed using an electric toothbrush directly into the wells. 0.26 KHz
- ➢ *Ultrasound*: was administered by using an ultrasonic jewelry bath cleaner. 40 KHz

Experimental Designs (Table 1)

1. Is there a difference between using distilled water or lipid solution as the solvent for Dextran?
2. Does sonication and ultrasound had a significant effect on Dextran crossing the microporous membrane?
3. Does sonication have a larger effect on permeability than the ultrasound?

Standard Curves

- ➢ Created standard curves with the Dextran in the lipid solution and distilled water using the serial dilution method (Dilution; Figure 2).
- ➢ We made two standard curves to determine whether the concentration of Dextran would vary drastically in water or lipid solution (Standard Curve; Figure 4).

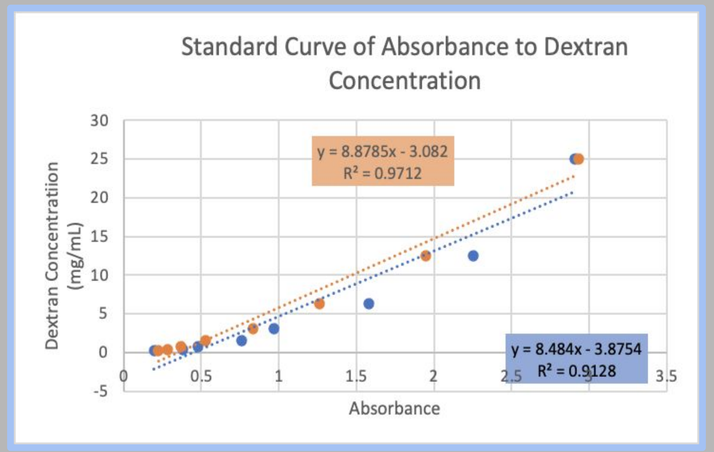


Figure 4: The orange standard curve represents the Dextran in lipid solution. The blue curve represents the Dextran in DI water. The equation for the orange line was used to calculate the Dextran concentration from absorbance of each of the wells in the experiment.

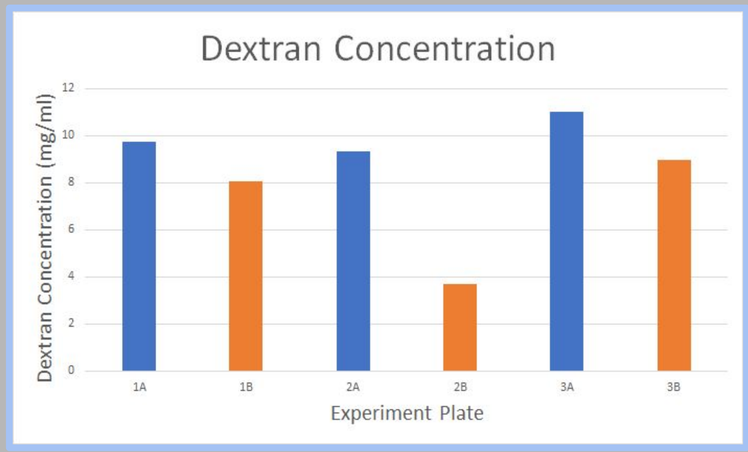


Figure 5: The A columns represent the experimental plates and the B columns represent the control plates for each experiment.

Table 1: Results of Each Experiment

	Plate	Dextran Solution	Sonicate?	Ultrasound?	Result (Dextran concentration mg/ml)
Exp 1	Experimental (1A)	Lipid	YES	YES	9.740
	Control (1B)	dH_20	YES	YES	8.056l
Exp 2	Experimental (2A)	Lipid	YES	YES	9.318
	Control (2B)	Lipid	NO	NO	3.710
Exp 3	Experimental (3A)	Lipid	YES	YES	10.998
	Control (3B)	Lipid	YES	NO	8.956

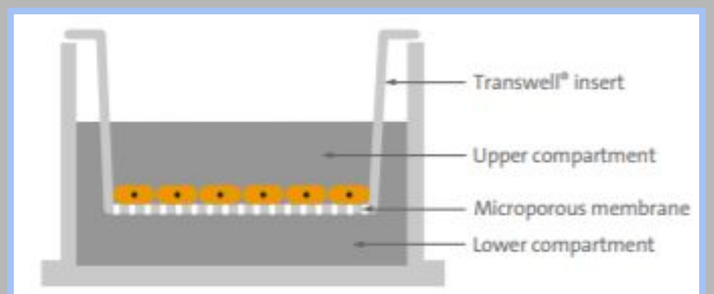


Figure 3: Distilled water was placed in the lower compartment of the well plate and the Dextran and liquid solution was placed in the upper compartment.

Literature Cited

(1) Herrup K. The case for rejecting the amyloid cascade hypothesis. Nature Neuroscience. 2015;18(6):794–799. doi:10.1038/nn.40179

Conclusion

- ➢ Overall, exposure to ultrasound/sonication along helped the Dextran get across the transwell membrane (Results; Table 1, Concentration; Figure 5).
- ➢ The utilization of microbubbles and ultrasound may be a helpful tool with administering certain drugs across an impermeable membrane, such as the blood brian barrier.
- ➢ In the future, this method could be used to deliver amaloid-beta antibodies to attach the plaques in an Alzheimer's patient's brain

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