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Eman Al Aboody

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Transporting ***Anti-amyloid*** Monoclonal ***Antibodies*** across the ***Blood-Brain Barrier*** using ***Focused Ultrasound Therapy*** to Slow down the Progression of ***Alzheimer's Disease***

Science as a Human Endeavour

Transporting Anti-amyloid Monoclonal Antibodies across the Blood-Brain Barrier using Focused Ultrasound Therapy to Slow down the Progression of Alzheimer's Disease

Introduction

Alzheimer's disease is a common neurodegenerative disease affecting 46 million people worldwide – a statistic expected to triple by 2050 (Ma, et al., 2023). Significantly impacting the aging population, Alzheimer's is characterised by toxic amyloid plaques in the brain which inhibit neurotransmission and cellular signalling, essentially killing neurons and shrinking the brain (The University of Queensland, 2022). It often results in cognitive deficits and memory loss (The University of Queensland, 2022). Some medications exist but are unable to independently pass through the blood-brain barrier, a highly selective membrane that protects the brain from toxins and concurrently limits the entrance of 98% of medications (Wu, et al., 2023) (Pardridge, 2012).

It was recently discovered that ***applying*** Focused Ultrasound Therapy, a revolutionary and innovative novel treatment method that slows down the progression of Alzheimer's disease combined with anti-amyloid monoclonal antibodies (medication) can increase the clearance of amyloid plaques in the brain. Focused Ultrasound Therapy breaches the blood-brain barrier temporarily allowing the efficacious delivery of Alzheimer's disease medications (Focused Ultrasound Foundation, 2024). While Focused Ultrasound Therapy can be ***applied*** to slow down the progression of Alzheimer's disease, the treatment method exhibits a few ***limitations*** and concerns that scientists are currently investigating. As a non-invasive and innovative approach, this treatment method has the potential to significantly benefit ***society*** and individuals with Alzheimer's ultimately increasing their quality of life and reducing the burden on healthcare systems.

Biological Background

Alzheimer's gradually deteriorates the brain and is characterised by the abnormal aggregation of beta-amyloid plaques and neurofibrillary tangles in the nervous system – beta amyloid proteins are chemically sticky compounds which accumulate in the brain and disrupt communication between neurons (fig. 1) (Stanford Medicine , 2024). These plaques begin as normal amyloid proteins that are typically produced by the brain except in Alzheimer's they fold incorrectly and accumulate outside of neurons (Reynaud, 2010). These abnormal aggregations are due to the accumulation of misfolded proteins which are toxic conformations and are considered to be the "molecular driver of Alzheimer's Disease pathogenesis and progression" (Zhang, 2023). In individuals diagnosed with Alzheimer's, damage initially appears in the hippocampus, an area in the brain responsible for the formation of memories where connections between neurons are destroyed (fig. 2) (Kakkad, 2023). After the discovery of beta-amyloid proteins which aggregate in the brain causing this neurodegenerative disease, various treatments have been attempted to inhibit the production and aggregation of this protein (Schnek , 2012). Enzymatic degradation, transport across the blood-brain barrier, glial cell phagocytosis are among the few strategies attempted that supposedly reduce the growth of amyloid proteins.

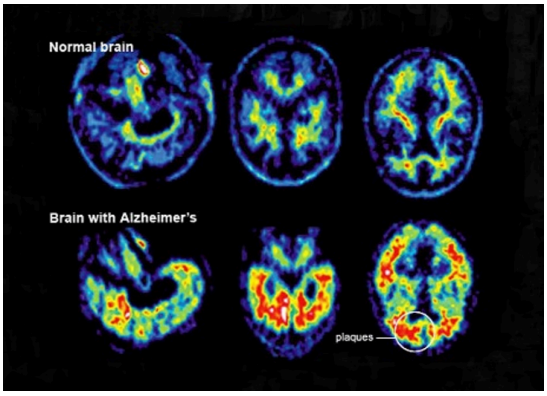

Figure 1 *(Yetman, 2023): PET scan comparing a normal brain and a brain with Alzheimer's. Individuals with Alzheimer's exhibit higher concentrations of amyloid plaque.*

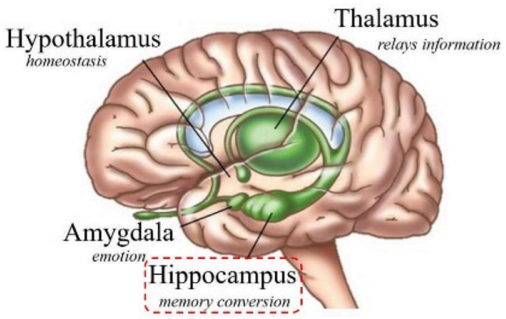

Figure 2 *(The Reign of the Brain, 2024): The brain's Limbic system consisting of the hippocampus (responsible for memory formation)*

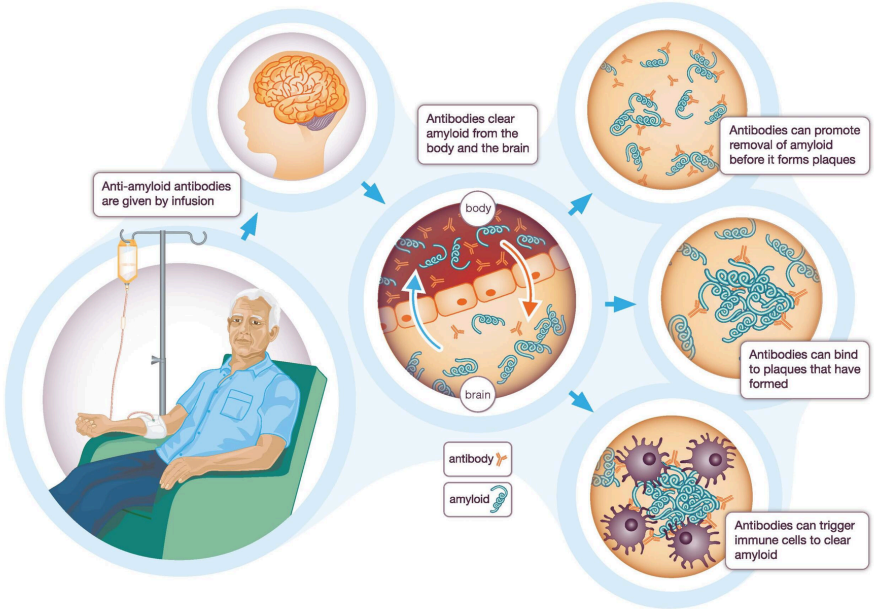

Figure 3 *(Yu, 2021): How Aducanumab targets amyloid plaque in Alzheimer's patients*

Biological Background

There is an interrelationship that exists between beta-amyloid plaques and low acetylcholine in Alzheimer's. Alzheimer's disease is characterised by a 90% reduction in acetylcholine neurotransmitters (Boston University School of Medicine, 1996). Acetylcholine is responsible for certain functions including memory and muscle contractions (Haam & Yakel, 2018). Furthermore, the physical presence of beta-amyloid plaques (which are chemically adhesive) in the brain can obstruct the transmission of acetylcholine from cholinergic neurons ultimately impairing synaptic transmission and resulting in cognitive deficits (Francis, 2005).

There are currently two FDA-approved anti-amyloid monoclonal antibodies in the market that assist with the clearance of brain plaque: aducanumab approved in 2021 followed by lecanemab in 2023 (fig 3 & 4). Both are delivered intravenously (injected into a vein using an IV/intravenous tube) with a treatment duration of 12-18 months. The treatment time is lengthy as these drugs struggle to pass through the blood-brain barrier (fig. 5). From a medical perspective, the Blood-Brain Barrier impedes the entry and transportation of 98% of drugs and pharmaceuticals (Pardridge, 2012) (Wu, et al., 2023).

The blood-brain barrier is a natural protective membrane that is semi-permeable and protects the central nervous system from toxins and pathogens that enter through the bloodstream (Wu, et al., 2023). Moreover, it obtains various mechanisms that control the influx and efflux of biological substances critical for the neuronal function and metabolic activity of the brain ultimately maintaining neuro-homeostasis (Kadry, et al., 2020). Endothelial cells are positioned extremely close to each other forming tight junctions which result in the blood-brain barrier's selective permeability allowing for the controlled passage of substances. The blood-brain barrier presents a significant limitation to the delivery of Alzheimer's medications such as anti-amyloid antibodies (McClure, 2023).

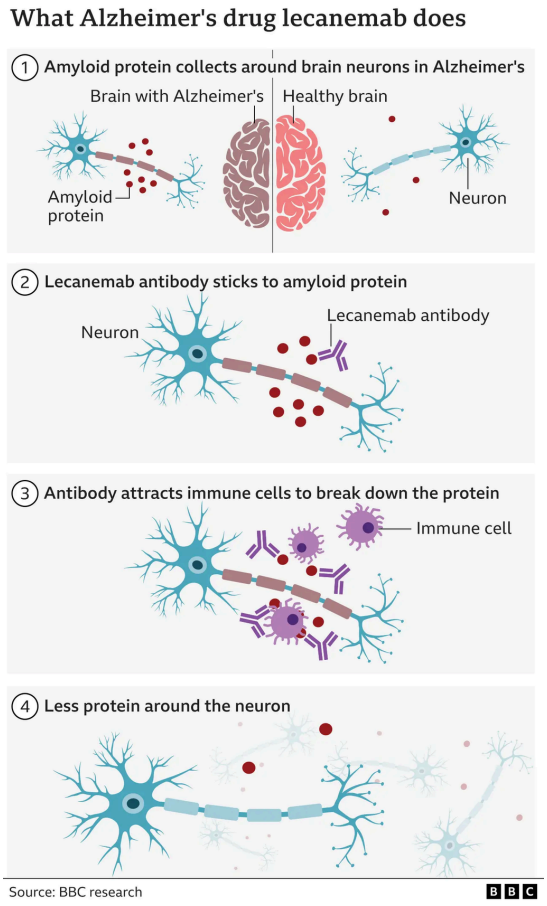

Figure 4 (Gallagher, 2022)

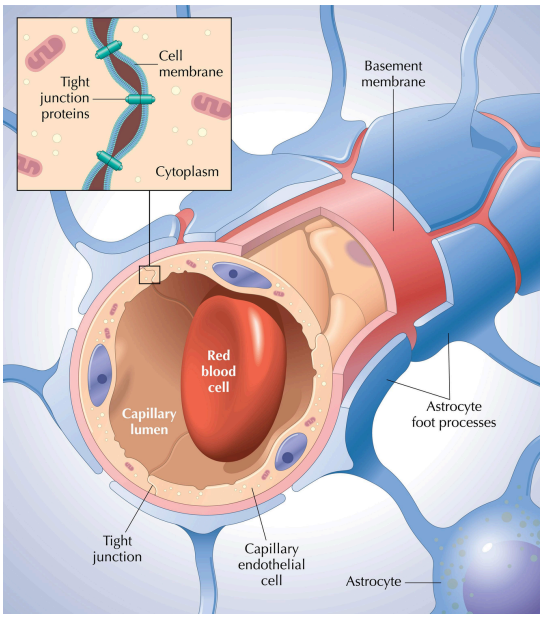

Figure 5 (Perkins, 2011): Structure of the blood-brain barrier

Applications

Applications of Using Focused Ultrasound Therapy to Transport Anti-amyloid Monoclonal Antibodies across the Blood-Brain Barrier

While there is no definitive cure for Alzheimer's, it is possible to delay the symptoms and progression of the disease using focused ultrasound therapy. As a matter of fact, applying a combination of focused ultrasound therapy and anti-amyloid medications can increase the rate of clearance of beta-amyloid plaques in Alzheimer's patients. As a non-invasive and therapeutic technology, it also exhibits a crucial mechanism involving temporary opening of the blood-brain barrier which can facilitate the delivery of anti-amyloid treatments responsible for removing beta-amyloid plaques from the brain across the blood-brain barrier for Alzheimer's patients (Focused Ultrasound Foundation, 2024).

As emphasised by the pioneer of this novel treatment technology Dr Ali Rezai, it is a cutting edge approach to brain surgery with no cutting or incisions in the brain. In focused ultrasound therapy, multiple beams converge which allows the ultrasound to produce therapeutic effects without incisions or radiations (fig 6, 7, & 8).

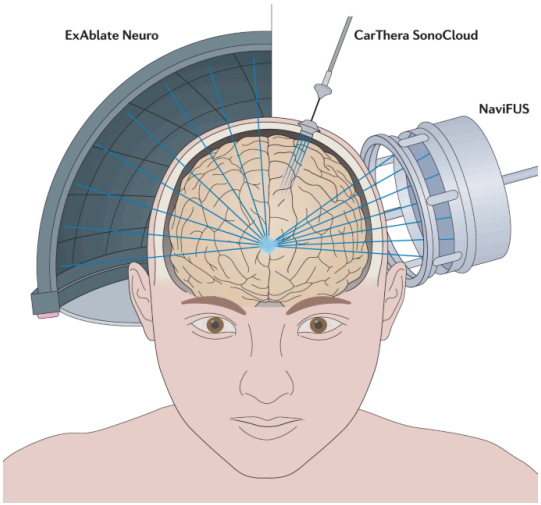

Figure 6 *(Meng, 2020): Multiple beams converging in Focused Ultrasound Therapy*

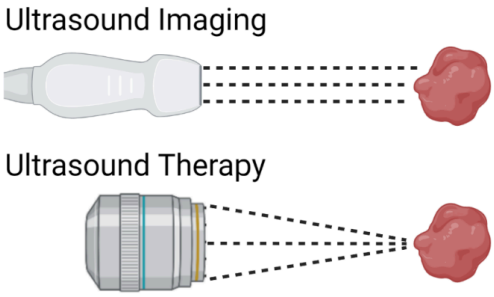

Figure 7 *(Wikipedia, n.d): "Ultrasound Imaging deposits energy over a large area while therapeutic ultrasound focuses the energy on one target site", therefore, increased accuracy in the treatment process (Wikipedia, n.d)*

Figure 8 *(Kolata, 2024): Alzheimer's disease patient undergoing focused ultrasound treatment*

Applications cont'd

Dr Ali Rezai originally ***applied*** his ***scientific knowledge*** demonstrated through ***testing*** focused ultrasound therapy to target the thalamus in the brain of patients with Parkinson's disease experiencing tremors (Johnson, 2021). After its success, Dr Rezai realised that focused ultrasound therapy can be ***applied*** and adapted to patients with other neurodegenerative disorders including Alzheimer's.

The process of Focused Ultrasound Therapy involves an IV solution containing microscopic bubbles of perfluorocarbon gas ranging from 1.1 to 3.3 microns that pry open the blood-brain barrier when hit with ultrasound energy (Kolata, 2024) (fig. 9). Low-frequency ultrasound pulses are focused and targeted on the area of the brain requiring treatment (normally the hypothalamus in Alzheimer's) (The University of Queensland, 2022). These pulses generate waves in the fluid of blood vessels allowing the microbubbles to vibrate, expand, and contract with the waves which temporarily opens the blood-brain barrier for 24-48 hours and then reseals which provides a tremendous opportunity for ant-amyloid antibodies and therapeutics to enter the brain successfully (Kolata, 2024) (60 Minutes, 2024). Patients that were given the treatments of ultrasound with infusion one a month over 6 months exhibited a 50% reduction in amyloid plaque than areas treated via infusion alone (60 Minutes, 2024).

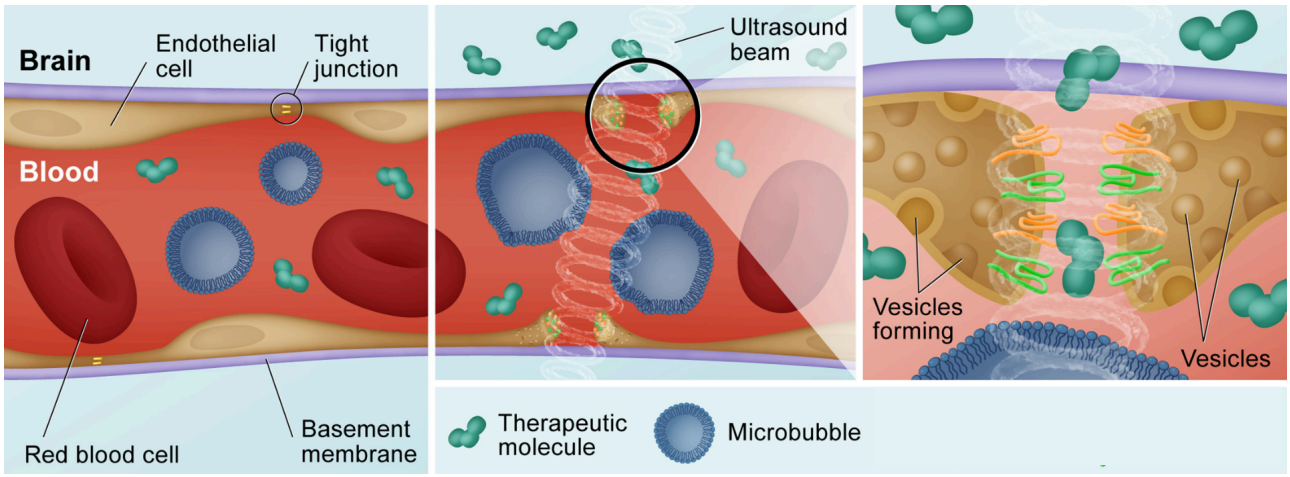

Figure 9 *(Yetman, 2023): Ultrasound beam microbubbles prying open the blood-brain barrier*

This promising scientific innovation in the field of medicine has the potential to not only improve the quality of life of patients with Alzheimer's but reduce ***economic outlay***. By shifting to this dual form of treatment via anti-amyloid antibodies and ultrasound, the costs saved from the current treatment plan for patients namely expensive consultations and aged care can be redirected to fund critical fields of research. This ***benefits*** not only patients who may come from low socioeconomic backgrounds but also the government and accelerates healthcare research, ultimately benefitting ***society***.

As previously stated, while the treatment strategy is still in its early stages, results show that focused ultrasound therapy exhibits great potential as biopharmaceuticals and drugs that were originally unable to cross the blood-brain barrier are now able to do so.

Limitations

Limitations of Using Focused Ultrasound Therapy to Transport Anti-amyloid Monoclonal Antibodies across the Blood-Brain Barrier

As with all emerging ***societal innovations*** in the field of medicine, transporting anti-bodies across the blood-brain barrier using focused ultrasound therapy to reduce amyloid plaque exhibits a few limitations and potential concerns. While the ultrasound device has been designed to deliver ultrasound to small and targeted areas in the brain, in some cases of Alzheimer's the beta amyloid plaque is located across the entire brain presenting a tremendous challenge (Kolata, 2024). The ***pilot study*** conducted by Dr Ali Rezai and his colleagues is not considered to be drastic enough to draw out any conclusions (Neergaard, 2024). Therefore, ***larger studies*** must be conducted to confirm the potential of this treatment strategy, ***providing opportunities*** for alternative innovations. Additionally, many of the anti-amyloid drugs have not been tested in broad groups of racial populations which limits the demographic of patient backgrounds who get diagnosed and treated with Alzheimer's disease, an area that must be further investigated (NEJM Group, 2024). Another ***limitation*** and ***concern*** for neurologists is that the process involves an increased rate of amyloid plaque reduction which could amplify the side effects resulting in bleeding and swelling in the brain (intracranial haemorrhage and cerebral oedema respectively) (Neergaard, 2024). It is vital that medical professionals undergo ***comprehensive testing***, ***monitoring***, ***assessment***, and ***further evaluation*** of risks to reduce these limitations and concerns to cater for an optimal treatment plan for patients in society diagnosed with Alzheimer's. Unfortunately, there is also an issue revolving around ***inequities*** in access to care. These drugs are all going to be given through IV therapy which does not exist in small, rural, hospitals. Already, ***disparities*** are beginning to emerge in Alzheimer's disease diagnosis and management which will be amplified – as a result, an aim should be to increase the ***availability*** of this treatment strategy to achieve ***social equity***.

Conclusion

Despite the ***limitations***, focused ultrasound therapy remains a promising area of research for the treatment of Alzheimer's disease with ongoing efforts to address challenges and improve its ***clinical application*** making a positive ***contribution*** to ***society*** by benefiting ***human health***. The method's "ability to disrupt the blood-brain barrier to effectively deliver treatment demonstrates the power and potential of using focused ultrasound technology when addressing complex neurological conditions" (Insightec, 2024). Furthermore, Focused Ultrasound Therapy exhibits potential for treating other neurodegenerative diseases and brain cancers using the delivery of chemotherapy drugs. Paving the way to a promising future of management for Alzheimer's disease, anti-amyloid antibodies and focused ultrasound therapy has the potential to revolutionise ***society's*** long-term ***geriatric healthcare*** of aging patients.

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