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COMMENTARY

Ultrasound blood–brain barrier opening: A new era of treatment for Alzheimer's disease?

Cuiping Wang[1,2,3] | **Junhong Ren**[1,2,3]

[1]Department of Sonography, Beijing Hospital, Beijing, China

[2]National Center of Gerontology, Beijing, China

[3]Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China

Correspondence
Junhong Ren, Department of Sonography, Beijing Hospital, Beijing, China.
Email: rjh18612300581@126.com

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The blood–brain barrier (BBB) plays an important role in maintaining the stability of the central nervous system (CNS). However, it serves as a formidable barrier that restricts the entry of therapeutic agents. Recent research shows that some pathways have the potential to reshape conventional drug delivery paradigms and address the limitations caused by the selectivity of the BBB. Innovative approaches to enhance drug delivery include intranasal delivery exploiting olfactory and trigeminal pathways, as well as techniques such as temporary BBB opening using chemicals and receptors, or focused ultrasound (FUS).[1] These technologies have their pros and cons. The intranasal delivery route is considered non-invasive, and drug transportation might proceed via the olfactory and trigeminal pathways, ultimately leading access to the CNS.[2] However, nasal administration exhibits certain limitations, such as the lack of consistency in the administered dosage of the drug.[3] Chemicals, such as borneol and alkyl glycerols, can enhance the permeability of the BBB, potentially revolutionizing drug delivery to the brain. However, consideration must be given to their potential toxicity and lack of selectivity. The second approach involves modifying tight junctions using adenosine receptor agonists, which has various advantages for drug administration across the BBB. Receptor-mediated modulation, owing to its inherent reversibility, has advantages of temporal regulation and adaptability during pharmaceutical administration.[4] The limitations of receptor-mediated tight junction transition include the absence of suitable receptors within the targeted region, the potential for unintended consequences for unrelated biological pathways or tissues, the inherent variability in receptor expression across the BBB, and the requirement for meticulous adherence to regulatory and safety protocols.[5] The third approach involves FUS to facilitate drug transport through the BBB. The application of FUS spans various domains, encompassing imaging, tumor ablation, neuromodulation, targeted gene therapy, and increasing drug delivery to the cerebral region.[1] Magnetic resonance imaging (MRI) guided FUS uses focused ultrasound energy, delivered transcranially, to treat a variety of neurological diseases, such as essential tremor (ET), Parkinson disease (PD), neuropathic pain, and dystonia.[6,7] A variety of neuropathic pain syndromes have been successfully treated using MRI-guided FUS central lateral thalamotomy.[6] MRI-guided FUS ventralis intermedius (VIM) thalamotomy is now a well-established and federal drug administration (FDA) approved therapy in medication-refractory ET and for the motor symptoms of PD. The use of concurrent MRI allows highly accurate spatial and thermal guidance, with fine anatomical detail, high soft-tissue contrast, and real-time monitoring of the treatment zone. MRI-guided FUS, temporarily targeting the BBB, can induce a controlled thermal elevation at the focal point, enabling a transient, localized, and reversible disruption of the BBB, thus aiding the delivery of targeted therapeutics or neuroimmune modulation. This technology has advantages such as precision, employment of non-ionizing radiation, and the capability for real-time temperature monitoring at the target site. However, its potential risks and safety measures still need to be considered.

Alzheimer's disease (AD) is one of the most common degenerative diseases of the CNS. Currently, there are approximately 46 million people living with AD worldwide, and the number is expected to triple by 2050, posing a huge challenge for health care.[8] At present, the recognized pathological mechanism of AD is the amyloid cascade

theory, characterized by the accumulation of amyloid-beta (Aβ) protein, which leads to senile plaques and neurofibrillary tangles within neurons. Recently, monoclonal antibodies against Aβ, including aducanumab, lecanemab, and donenemab, have proven to be effective against AD.[9] In the issue of the New England Journal of Medicine published on January 4, 2024, Rezai et al.[10] reported a proof-of-concept trial involving three participants with mild AD, which assessed the safety and feasibility of combining an aducanumab infusion with MRI-guided FUS to penetrate the BBB and target Aβ in AD. The trial involved small tissue volumes in one side of the brain of three participants. The protocol treatment was divided into two phases: An intervention phase, which combined FUS to open the BBB at the time of aducanumab treatment for 6 months, and a follow-up phase, in which the participants received aducanumab infusion alone for 5 years. This study revealed a modest decrease in Aβ levels, quantified using fluorine-18 florbetaben in positron emission tomography (PET), and there was no cognitive worsening during the 6-month combined-treatment phase. In the three participants, a more significant decrease in Aβ levels (ranging from 48% to 63%) was noted in areas targeted by FUS compared to identical, untreated brain regions on the opposite side during the combined treatment phase. Earlier research indicated that the application of FUS alone marginally lowered Aβ levels. Experimental models demonstrated that FUS usage led to a five- to eight-fold increase in the delivery of aducanumab to targeted brain areas compared with that in regions not treated with FUS.[11,12] However, Rezai et al.[10] confirmed that during the follow-up phase, two of the participants experienced no neurological, cognitive, or behavioral changes. Only one participant exhibited cognitive decline; however, no alterations were noted in their neurological status or daily living activities. It is difficult to determine whether these cognitive changes are related to the disease or the procedure, mainly because of the small number of participants. Further clinical studies are needed for confirmation.

With regard to adverse reactions, Rezai et al. noted that headaches were the most frequent side effects, but were generally mild, with one instance of a moderate headache. The treatment was not associated with infarction, edema, demyelination, bleeding, or gliosis. In another phase 1 trial, 5 patients with AD were treated by MRI-guided FUS to open the BBB. Using less than 1% of the energy required for ablation, the BBB along the frontal white matter was successfully confirmed, and the target area was enhanced by local gadolinium extravasation, which proved to be reproducible, with no serious adverse effects.[13] Another study aimed to evaluate the efficacy and safety of MRI-guided FUS in PD via a systematic review and meta- analysis of 20 studies involving 258 patients from 2014 to 2023, which showed that MRI-guided FUS provided an effective and relatively safe treatment option for patients with drug-resistant PD-related tremor.[14] Therefore, MRI-guided FUS can safely and reversibly breach the BBB without causing severe adverse events.

The strategy of using FUS to open the BBB to allow drug delivery to treat AD has seen broadly implemented in preclinical settings, with its clinical utility being explored in early stage AD.[15] Despite these advances, much remains to be accomplished in refining its application. Primarily, enhanced clinical trials are essential to optimize drug dosing, the frequency and extent of FUS sessions, and the selection of target brain areas. Furthermore, while FUS technology continues to evolve, it is predominantly integrated with costly MRI systems, limiting its wider clinical uptake. This limitation encourages the pursuit of simpler, quicker, safer, and more cost-effective alternatives. Notably, the advent of portable, neuronavigation-guided FUS systems presents a less expensive and more efficient choice, potentially widening FUS accessibility for AD and other neurological conditions at various care points.[9] Additionally, while targeting Aβ alone does not reverse the disease, FUS, akin to pharmaceutical approaches for AD, falls short of entirely reversing the disease in the advanced stages. Nonetheless, early intervention using FUS in AD, particularly at the asymptomatic or initial phases, might postpone disease progression.[16] The limited effectiveness of late-stage treatments juxtaposed with the encouraging outcomes from early interventions, warrants deeper exploration into the preventive capacity of FUS in pre-symptomatic Alzheimer's stages.

Taken together, the available studies support a possible role for FUS in the treatment of AD. Future studies are warranted to determine the safety and feasibility of using FUS to delay the onset of the cognitive and pathological effects of AD. With advances in this field, we believe that FUS will provide innovative directions and insights for AD therapy.

AUTHOR CONTRIBUTIONS

Drafting of the manuscript: C.W. Critical revision of the manuscript for important intellectual content: J.R. Administrative, technical, or material support: J.R. Study supervision: J.R.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

ORCID

Cuiping Wang https://orcid.org/0000-0002-4178-5452

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