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Magnetic Resonance-Guided Focused Ultrasound : Current Status and Future Perspectives in Thermal Ablation and Blood-Brain Barrier Opening

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Magnetic resonance-guided focused ultrasound (MRgFUS) is an emerging new technology with considerable potential to treat various neurological diseases. With refinement of ultrasound transducer technology and integration with magnetic resonance imaging guidance, transcranial sonication of precise cerebral targets has become a therapeutic option. Intensity is a key determinant of ultrasound effects. High-intensity focused ultrasound can produce targeted lesions via thermal ablation of tissue. MRgFUS-mediated stereotactic ablation is non-invasive, incision-free, and confers immediate therapeutic effects. Since the US Food and Drug Administration approval of MRgFUS in 2016 for unilateral thalamotomy in medication-refractory essential tremor, studies on novel indications such as Parkinson's disease, psychiatric disease, and brain tumors are underway. MRgFUS is also used in the context of blood-brain barrier (BBB) opening at low intensities, in combination with intravenously-administered microbubbles. Preclinical studies show that MRgFUS-mediated BBB opening safely enhances the delivery of targeted chemotherapeutic agents to the brain and improves tumor control as well as survival. In addition, BBB opening has been shown to activate the innate immune system in animal models of Alzheimer's disease. Amyloid plaque clearance and promotion of neurogenesis in these studies suggest that MRgFUS-mediated BBB opening may be a new paradigm for neurodegenerative disease treatment in the future. Here, we review the current status of preclinical and clinical trials of MRgFUS-mediated thermal ablation and BBB opening, described their mechanisms of action, and discuss future prospects.

Key Words : Alzheimer disease · Blood-brain barrier · Essential tremor · High-intensity focused ultrasound ablation.

INTRODUCTION

Magnetic resonance-guided focused ultrasound (MRgFUS) is an emerging technique that uses acoustic energy delivered through the skull to treat intracranial diseases. In the early 1950s, William Fry and colleagues first developed high-intensity focused ultrasound (HIFU) as a neurosurgical tool to treat symptoms associated with Parkinson's disease[29,42-45,83]. Through early explorations with the feline brain, they discovered that high-intensity ultrasound could be precisely focused to create a distinct, thermal coagulative lesion in the brain without damaging the intervening tissue[42,83]. However, at that

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time, widespread clinical application of HIFU as neurotherapeutic tool was limited, because ultrasound transducers were insufficiently powered to penetrate the skull and thus craniectomy was required to avoid absorption and reflection of ultrasonic energy at the bony interface[29,39,43-45,82]. In the late 1990s, a completely non-invasive FUS treatment was realized consisting of a head-mounted set of phase-array transducers arrays operating under real-time magnetic resonance imaging (MRI) guidance[49,82]. Software was also incorporated into the device to rectify phase aberrations due to skull thickness, based on pre-obtained computed tomography scans, enabling multiple ultrasonic waves to converge at single focus[26,39]. Furthermore, simultaneous MR thermometry provided real-time temperature monitoring, enabling confirmation that the target zone has been reached with the proper thermal dose[39,49]. To couple energy delivery to the scalp, cooled degassed water (15–20℃) was circulated in a silicone rubber diaphragm tightly placed around the patient's head[39]. In 2016, the US Food and Drug Administration (FDA) approved HIFU thalamotomy as a treatment for medication-refractory essential tremor (ET), and ablative HIFU is now being investigated for the treatment of movement disorders such as Parkinson's disease (PD), and in an ever-widening set of neurological diseases including psychiatric disease and brain tumors[20,34,54,72,79,84]. Meanwhile, blood-brain barrier (BBB) opening by delivering pulsed ultrasound to microbubble-enriched cerebral vasculature has been under active investigation in the hope of enhancing drug delivery to the brain for the treatment of intracranial disease[14,24,36]. Here we review the current status and prospects of MRgFUS clinical applications in neurosurgical field in terms of thermal ablation and BBB opening and discuss the direction and challenges of MRgFUS research in the future.

THERAPEUTIC MECHANISMS OF ULTRASOUND IN THE CENTRAL NERVOUS SYSTEM

Ultrasound is defined as an acoustic wave with fundamental frequency above the upper limit of human hearing (>20 kHz). Ultrasound frequencies for medical imaging range between 2–20 MHz, while those for therapeutic applications are lower (0.2–2 MHz)[106,109,110]. Ultrasound used in treatment is categorized into two types based on its intensity, which is defined as the total power delivered divided by the beam area at the focal region (W/cm^2). Depending on the intensity, ultrasound has different biophysical actions on tissues[112,118]. HIFU requires an intensity greater than 1000 W/cm^2, which induces thermal ablation of tissue at the focal region. HIFU in continuous mode induces frictional energy in the target area so that the target tissue is heated, causing protein denaturation, DNA fragmentation, coagulative necrosis, and cellular death[1,11,28,32]. Meanwhile, intervening tissues such as scalp, skull, cerebrospinal fluid, and superficial structures receive unfocused ultrasonic waves with intensities lower than the heating threshold of tissues[39,47,61,92]. HIFU delivered at ~300 W/cm^2 has also been shown to suppress neuronal activity by disrupting synaptic contacts[11,118]. However, as HIFU at various intensities can eventually result in permanent tissue damage, its application for neuromodulation is suboptimal[29]. In contrast, low-intensity focused ultrasound (LIFU) has been shown to modulate activity of neurons and glial cells, and is typically pulsed, with FDA limits of time-averaged intensities ≤94 mW/cm^2 and pulse-averaged intensities <190 W/cm^2 [33,40,88]. Depending on key pulsing parameters such as pulse repetition frequency and duty cycle, pulsed LIFU can either suppress or evoke neuronal activity. One proposed neurostimulatory mechanism is that acoustic radiation forces and pressure mechanically stretch the lipid bilayer of neurons and thereby open voltage-gated ion channels with mechanosensitive properties, including Na^+, Ca^{2+}, and K^+ channels, which in turn results in depolarization and neuronal excitation[55,86,119] (Fig. 1). An additional potential theory is that alterations in the membrane permeability to ions triggered by the mechanical force of LIFU is speculated to result in local membrane depolarization which in turn stimulates voltage-gated ion channels[118,119]. Neuroinhibitory mechanisms of LIFU are also thought to be stretch-mediated, but the excitatory or inhibitory effects of LIFU on neurons differs depending on the ultrasound parameters[15]. These neuromodulatory properties of pulsed LIFU makes FUS appealing as a non-invasive neuromodulation method[40]. Although several non-invasive neuromodulating technologies such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation have been employed, they suffer from drawbacks such as poor spatial resolution and poor depth penetration[15,68]. Conversely, FUS has high spatial specificity, with a focus of a few millimeters in diameter, and is able to reach deep brain targets due to advances in transducer focusing technology. In addition, unlike rTMS, the si-

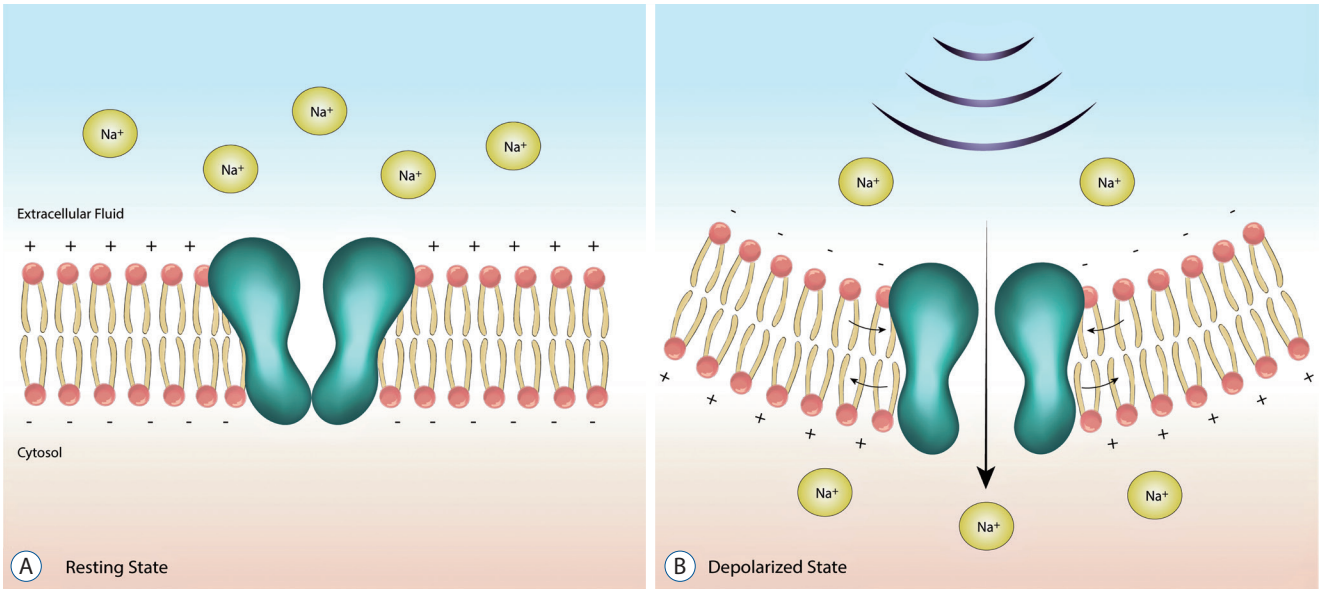

Fig. 1. Schematic depicting proposed pulsed LIFU neuromodulation mechanism. A : Resting state of neuron without ultrasound. B : Depolarized state with ultrasound. The mechanical force of ultrasound wave changes neuronal lipid bilayers tension. Voltage-gated ion channels, including Na^+, Ca^{2+}, and K^+ channels, with mechanosensitive properties, open in response to pulsed LIFU, which leads to depolarization and generation of action potentials, eventually stimulating neurons. Here, Na^+ channels are depicted as an example. LIFU : low-intensity focused ultrasound.

multaneous use of FUS and functional MRI is feasible, enabling high-spatial resolution brain mapping[15,68]. Meanwhile, at higher energies, pulsed LIFU has the important characteristic of being capable to produce stable oscillation of microbubbles, which transiently opens the BBB by separating the endothelial tight junction, enhancing the localized delivery of therapeutic agents including antibodies, growth factors, nanoparticles, nucleic acid, viral vectors, and cells to the brain[39,65,105] (Fig. 2). Initially, HIFU had been applied for BBB opening, however, high intensities risk giving rise to thermal coagulation of tissue and undesirable inertial cavitation, which result in permanent tissue damage or gross hemorrhage[120,121]. To avoid these adverse effects, in 2001, Hynynen et al.[50] applied LIFU, instead of HIFU, in conjunction with intravenously administered preformed microbubbles for BBB opening. As preformed microbubbles pass through the ultrasound field, they oscillate at the same frequency as ultrasound waves, resulting in stable contraction and expansion. This stable cavitation of microbubbles is thought to concentrate the ultrasonic energy and impart mechanical force to the cerebral vasculature, enabling transient, safe, and reproducible BBB disruption at low frequencies[50,51,81]. Ultrasound produces periodic pressure variation in biological tissues as it transmits, triggering the formation and oscillation of small gas filled cavities (i.e., microbubbles) in the tissue fluids[91,118]. Two types of cavitation are generated by the ultrasound wave depending on its intensity (Fig. 3). First, inertial cavitation is created when microbubbles exposed to HIFU, violently collapse after expanding nonlinearly[118]. Inertial cavitation can damage tissues by inducing extremely high temperatures, jet streams, and high concentration of free radicals in the tissue[29,106,110]. A second type of stable cavitation achieved when the microbubbles are subjected to pulsed LIFU, is more benign since the bubbles do not violently explode or collapse[15,100,118].

CLINICAL APPLICATION OF HIFU ON THERMAL ALBALTION

Stereotatic lesioning

MRgFUS has been investigated most commonly in movement disorders. Lesioning via stereotactic radiofrequency (RF) ablation has effectively alleviated movement disorder symptoms in ET, PD, and dystonia. Therefore, it was thought that lesioning using HIFU would work in a similar way in these diseases. Contrary to conventional RF lesioning methods, lesioning via MRgFUS is noninvasive, that is, no incision, no burr hole trephination, and no electrode insertion are re-

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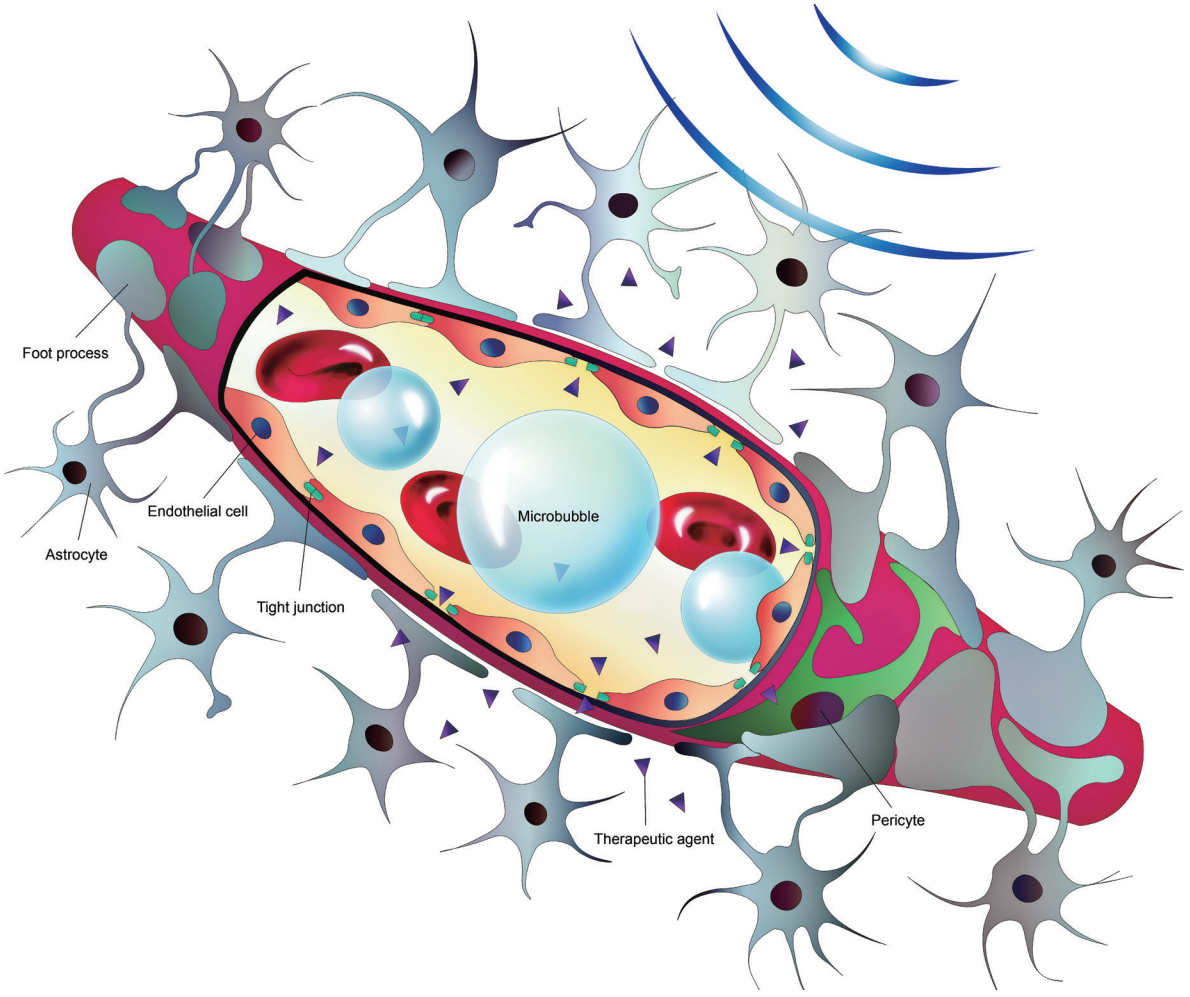

Fig. 2. Schematic illustration of transient BBB opening. MRgFUS in conjunction with microbubbles leads to open the BBB by separating the endothelial tight junction, allowing enhanced delivery of therapeutic agents. BBB : blood-brain barrier, MRgFUS : magnetic resonance-guided focused ultrasound.

quired. Moreover, as stereotactic targets of movement disorder are located near the center of the skull, it is feasible to make a discrete lesion at the target while minimizing thermal damage to the overlying skull and scalp. In addition, since the procedure is performed in awake patients and in a stepwise fashion, immediate clinical feedback is available from the patients, encouraging the application of MRgFUS to movement disorders. Since MRgFUS unilateral thalamotomy in medication-refractory ET patients was approved by FDA in 2016, its application has bloomed, and clinical indications have expanded. MRgFUS uses a protocol for lesioning which is transferable across its many clinical indications. First, escalating doses of low-power sonication are applied to raise target temperatures to around 45℃, below the threshold leading to coagulation necrosis. At this time, radiological evaluation of thermal lesioning location and clinical evaluation for safety is performed. After accuracy at the desired target is determined, several high-power sonications are applied under the guidance of MR thermometry, gradually escalating the acoustic power and energy until the temperature at the target reaches 55–60℃[72,76]. MRgFUS parameters across various intracranial applications are summarized in Table 1.

Essential tremor

ET is the most common movement disorder affecting 4% of the population over 40 years old, characterized by postural and intentional tremors at 8–12 Hz[34,82]. The primary treatment for ET is medication such as propranolol and primidone, but surgical treatment targeting the ventral intermediate nucleus (Vim) of the thalamus may be considered in patients

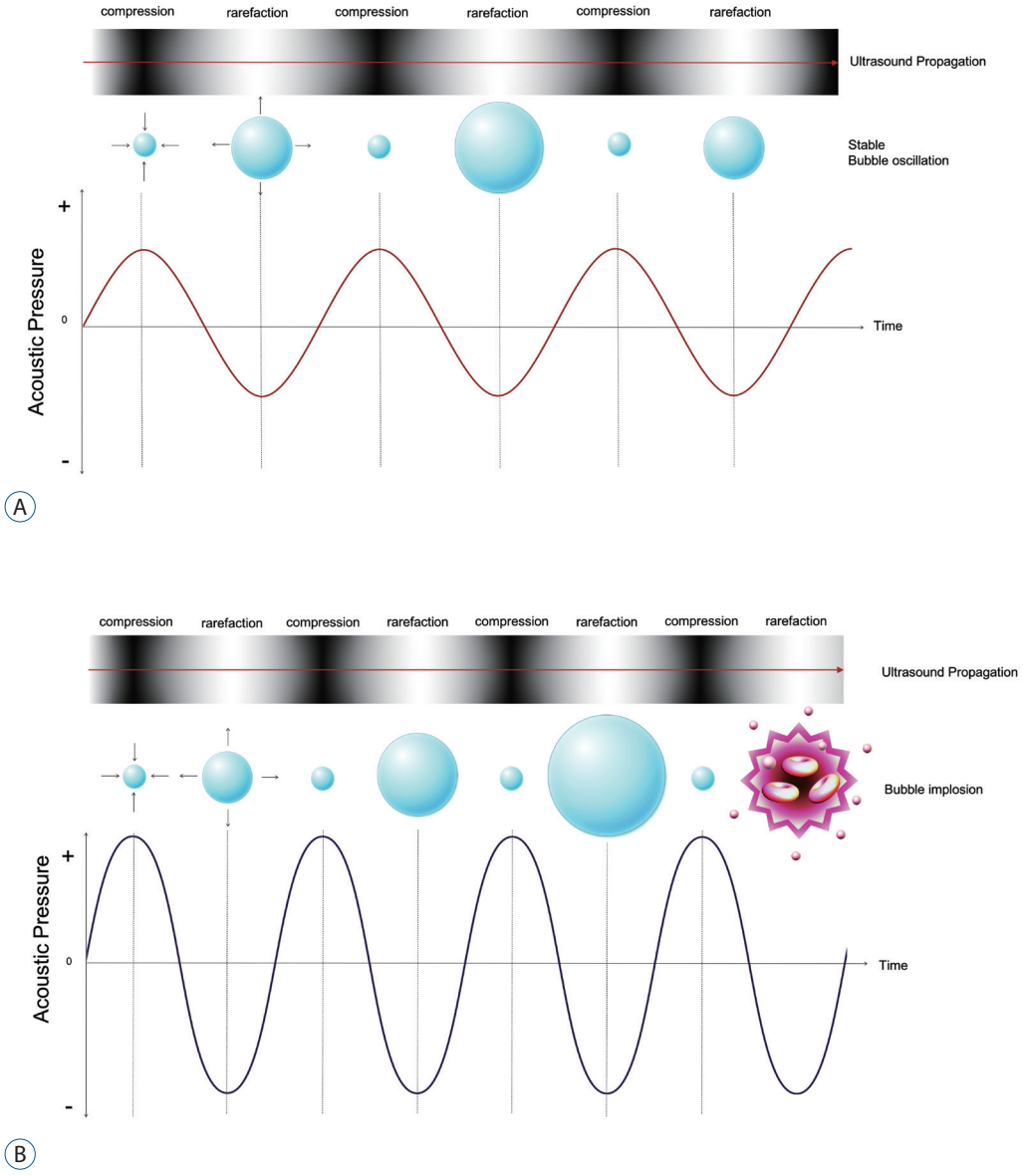

Fig. 3. A : Schematic illustration of stable cavitation. As the acoustic wave propagates longitudinally, it alternates between compression and expansion, with changing acoustic pressures along the sinusoidal curve. When microbubbles are subjected to pressures below the inertial cavitation threshold, they contract during compression and expand during rarefaction, resulting in stable oscillation. B : With ultrasonic pressure above the inertial cavitation threshold, microbubbles initially oscillate but eventually implode at rarefaction pressure.

who are refractory or intolerant of medication. RF ablation, radiosurgery, or deep brain stimulation (DBS) are options that may be considered for the patients[82,89,127]. The first two pilot studies of MRgFUS thalamotomy were published in 2013. One proof of concept study, in which four ET patients were enrolled, showed favorable outcome of 81.3% reduction of tremor in the dominant hand and 51.1% reduction in functional disability, as measured on the Clinical Rating Scale for Tremor (CRST) score, at 3 months after surgery[72]. Another study was performed in 15 patients and also demonstrated promising results of significant improvement of the contralateral hand tremor by 75% (p=0.001) and functional disability related to tremor by 85% (p=0.001) at 12 months after surgery[34]. A subsequent randomized trial in 76 patients (20 sham-treated pa-

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Table 1. MRgHIFU parameters in various intracranial disease applications

Study	Application	Disease	Number of patients	Parameters of sonication				Max temp (℃) at focus
				Frequency	Number of Sonications	Duration per sonication	Max acoustic power or energy per sonication	
Elias et al.[34] (2013)	Vim thalamotomy	ET	15	650 kHz	18 (11–26)	10–20 seconds	10320 J (6500–20800)	58.4 (54–63)
Chang et al.[19] (2018)	Vim thalamotomy	ET	76	650 kHz	18.5	10–20 seconds	14497 J (3500–34860)	55.6±2.3
Zaaroor et al.[128] (2018)	Vim thalamotomy	ET or TDPD	30	650 kHz	21 (14–45)	13–24	12500J (5850–23040)	56.5 (55–60)
Bond et al.[10] (2017)	Vim thalamotomy	TDPD	27	710 kHz	13.2	NA	8977 J (>50℃)	52.4
Magara et al.[76] (2014)	Pallidothalamic tractotomy	PD	13	710 kHz	4–5 at peak ℃	10–21	1200 W/20400 J	56.2 (52–59)
Martínez-Fernández et al.[77] (2018)	Subthalamotomy	PD	10	NA	23 (16–39) in total 8 (4–12) >55℃	144–379 seconds in total	14624 J (7200–36680)	57
Kim et al.[63] (2018)	Bilateral capsulotomy	OCD	11	650 kHz	(23–37)	>3 seconds at a peak ℃	NA	51–65
Jeanmonod et al.[54] (2012)	Central lateral thalamotomy	CNP	12	650 kHz	NA	10–20 seconds	800–1200 W/12000 J	51–64
McDannold et al.[79] (2010)	Tumor ablation	GBM	3	670 kHz	12, 16, and 17	20 seconds	650W (patient 1 and 3) 800 W (patients 2)	42, 51, and 48
Coluccia et al.[27] (2014)	Tumor ablation	Recurrent GBM	1	650 kHz	25	10–25 seconds	150–950 W/19950 J	65
Monteith et al.[84] (2013)	Thrombolysis Laboratory	ICH	5 swine; 5 cadavers	230 kHz	(2–3)	30 seconds	1500 W for swine with skull 750 W for swine without skull 3950 W for cadavers	6 (4–11)
Alkins et al.[4] (2013)	CSF diversion Laboratory	oHCP	9 swine	650 kHz 230 kHz	NA	0.1–5 seconds	1000–2200 W for 650 kHz 2900 W for 230 kHz	No significant

Values are presented as mean (range). MRgHIFU : magnetic resonance-guided focused ultrasound, Vim : ventral intermediate nucleus, ET : essential tremor, TDPD : tremor-dominant Parkinson's disease, NA : not applicable, PD : Parkinson's disease, OCD : obsessive-compulsive disorder, CNP : chronic neuropathic pain, GBM : glioblastoma multiforme, ICH : intracerebral hemorrhage, CSF : cerebrospinal fluid, oHCP : obstructive hydrocephalus

tients) with ET confirmed the efficacy of MRgFUS thalamotomy with improvement of hand tremor score by 47% and by 62% reduction in disability score at 3 months[35]. Recently, the same group has reported the long-term robustness of MRgFUS thalamotomy[19]. At 2 years after surgery (67 patients), the mean hand tremor and functional disability scores improved by 56% and 60%, respectively, with two patients reporting complete resolution of hand tremor. Commonly reported acute adverse effects included numbness/paresthesia (38%), taste disturbances, headache, and ataxia[21,58,97,128]. The vast majority of side effects recovered within 3 months after treatment[21,48,58,128]. Long-term side effects persisting at 2 years included gait disturbance, dysgeusia, dysmetria, muscle weakness, and dizziness, while all events were reported mild to moderate[19]. The adjustable and titratable properties of DBS have certain advantages over lesioning surgery[111]. However, DBS is an invasive procedure that can be associated with infection (1–3%) or hemorrhage (0.5–2.0%), and hardware problems including electrode migration, fracture (1–3%), and malfunction (1–3%)[38,39,96,108]. Also, DBS patients with primary cells require periodic replacement of the implanted pulse generator when the batteries are depleted. GammaKnife radiosurgery (GKRS) is another non-invasive technique for lesioning but can be associated with some unpredictability of the response and delayed effects of radiation, often requiring weeks to months to detect a clinical benefit[39,82]. Moreover, since it is not possible to monitor the patients' clinical symptoms during the procedure, determining an optimized target with GKRS can be challenging. Several clinical trials are underway to further evaluate the effectiveness and safety of MRgFUS

unilateral thalamotomy (NCT01827904, NCT02289560, NCT03253991). The current status of clinical investigation of MRgFUS in various intracranial diseases is presented in Table 2.

Parkinson's disease

PD is another main indication for MRgFUS. The success of MRgFUS-mediated Vim thalamotomy trials in ET patients inspired investigators to target the Vim in tremor-dominant PD patients[37,102,128]. Zaaroor et al.[128] reported that in 9 tremor-dominant PD patients undergoing MRgFUS Vim thalamotomy, the total motor Unified Parkinson's Disease Rating Scale (UPDRS) score improved by 46.2% at 6 months after surgery, while resting and postural tremors (assessed by the item 20 and 21 of UPDRS) alleviated by 90% and 80%, respectively (NCT03300193). A randomized double-blind sham-controlled study in 27 patients (seven sham-treated patients) followed up to 1 year also demonstrated long-term efficacy of MRgFUS Vim thalamotomy in tremor-dominant PD (NCT01772693)[10]. On medication, the CRST score improved by 62% following MRgFUS thalamotomy versus 22% after sham procedure at 3 months after surgery, while motor UPDRS score improved by 35% versus 4% after MRgFUS thalamotomy and sham procedure, respectively, at 3 months after surgery. At 1 year, 65% of patients (13 out of 20) had a positive outcome, defined as at least 50% reduction in the on-medication hand tremor subscores of the CRST from a baseline. At 1-year follow-up, paresthesia remained in 19% of patients, while 4% reported persistent ataxia. Further long-term studies are needed to determine

Table 2. Current status of clinical trials of MRgHIFU treatment in neurological diseases

Indication	Stage	Disease subtype	Target	Status
Essential tremor	Phase II		Unilateral Vim	One phase II trial published (NCT01827904) other phase II trials currently being conducted (NCT01827904, NCT02289560) and recruiting patients (NCT03253991)
Parkinson's disease	Phase I	Tremor-dominant	Unilateral Vim	Several trials published (NCT02252380[37], NCT03300193[102,128], NCT01772693[10])
		Levodopa-induced dyskinesia	Unilateral GPi	Currently conducting trials and recruiting patients (NCT02347254, NCT02003248, NCT02263885, NCT03319485)
		Akinesia-dominant	Unilateral STN	One phase I trial published (NCT02912871), currently conducting trials (NCT02246374) and recruiting patients (NCT03454425)
Psychiatric disease	Phase I	Major depressive disorder	Bilateral ALIC	Case report published and recruiting patients (NCT03421574, NCT02348411)
		Obsessive-compulsive disorder	Bilateral ALIC	One phase I trial published currently conducting trials (NCT01986296) and recruiting patients (NCT03156335)
Pain syndrome	Phase I	Neuropathic pain	Central lateral thalamic nucleus	One published[54] and continuing to recruit patients (NCT03255395)
		Trigeminal neuropathic pain	Bilateral medial thalamic nucleus	Currently recruiting patients (NCT03309813)
Epilepsy	Phase I	Secondary epilepsy due to subcortical lesion	Subcortical lesion	Currently recruiting patients (NCT02804230)
		Generalized	Anterior thalamic nucleus	Currently recruiting patients (NCT03417297)
Brain tumor ablation	Phase I	Malignant		One study completed (NCT01698437) and now recruiting patients (NCT01473485, CT00147056)
		Benign	Centrally located	Now recruiting patients (NCT03028246)
Thrombolysis/ intracerebral hemorrhage	Preclinical			Swine and cadaveric models demonstrated feasibility of ICH liquefaction[85]
CSF diversion	Preclinical		Floor of third ventricle	Providing proof-of-principle of MRgHIFUS- mediated third ventriculostomy[4]

MRgHIFU : magnetic resonance-guided focused ultrasound, Vim : ventral intermediate nucleus, GPi : globus pallidus interna, STN : subthalamic nucleus, ALIC : anterior limb of internal capsule, ICH : intracerebral hemorrhage, CSF : cerebrospinal fluid

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whether MRgFUS thalamotomy for PD has lasting effectiveness and if patient side effects eventually resolve. The globus pallidus interna can be another important target for MRgFUS. In an early report of MRgFUS unilateral pallidotomy in a PD patient suffering from severe dyskinesias, the motor UPDRS score in on-medication state was reduced by 60% at 6 months after surgery, whereas score in the off-medication state was reduced by 55%[87]. The unified dyskinesia rating scale score was also significantly improved by 70% at 6 months postoperatively. Several clinical trials of MRgFUS unilateral pallidotomy are in progress (NCT02003248, NCT02263885, NCT02347254, NCT03319485). Because of the high incidence of adverse effects with bilateral lesions, MRgFUS pallidotomy has been limited in only one hemisphere[52,107]. Meanwhile, despite the subthalamic nucleus (STN) is a well-established DBS target, stereotactic lesioning surgery targeting the STN had been limited because of concerns about incidence of postoperative involuntary movement such as hemichorea and hemiballismus, which were reported as high as 15%[6,39,67]. However, subthalamotomy with FUS is being examined[39]. A pilot study of unilateral subthalamotomy using MRgFUS in 10 patients has recently reported that motor UPDRS scores improved by 53% in the off-medication state and by 47% in the on-medication state at 6 months after surgery[77]. Over 6 months follow-up, a total of 38 adverse events were recorded, including three persisting events that were directly STN-related, namely, off-medication choreic dyskinesia, on-medication non-disabling dyskinesia, and subjective speech disturbance. The two aforementioned patients suffering from involuntary movements after subthalamotomy had resolution of symptoms by 6 months postoperatively after adjusting medication. Currently, other phase I subthalamotomy studies are also underway (NCT02246374, NCT03454425) (Table 2).

Psychiatric disease

The feasibility of MRgFUS in obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) is being investigated. A common surgical target in treatment-resistant patients include the anterior limb of the internal capsule (ALIC)[41,82]. ALIC fiber tracts carry information between the limbic cortices and thalamus and are thought to be associated with mood and anxiety disorders[25,60,103]. The first reported clinical trial for MRgFUS bilateral capsulotomy was completed in in four medically refractory OCD patients[58]. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score gradually improved by 33% over 6-month follow-up period, while Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A) scores were immediately relieved by 61.1% and 69.4%, respectively, after surgery in all patients and such effects were sustained during the same period. A recent study by the same group in 11 OCD patients has shown that the above-mentioned clinical effects were maintained for 2 years, with Y-BOCS, HAM-D, and HAM-A scores being improved by 38%, 60%, and 65%, respectively[63]. Meanwhile, the first MRgFUS lesioning for MDD was also performed with the ALIC as the target, reporting significant improvements of HAM-D and Beck Depression Inventory scores by 73% and 54%, respectively, at 12 months after surgery[62]. Clinical trials (NCT02348411, NCT03421574) are underway to further evaluate the safety and initial effectiveness of MRgFUS bilateral capsulotomy for medically refractory MDD patients.

Chronic neuropathic pain

In chronic neuropathic pain, RF ablative surgery of the central thalamus has been successfully performed in medication-refractory patients, spurring the application of MRgFUS to this condition[123,126]. One study that performed MRgFUS-mediated central lateral thalamotomy reported mean pain relief of 57% at 12 months follow-up in eight patients[54]. Clinical trials continue to investigate the effects of MRgFUS thalamotomy for chronic neuropathic pain (NCT03255395, NCT03309813)[82].

Epilepsy

Pilot studies are underway for MRgFUS-mediated ablation for epilepsy : one study aims to ablate subcortical lesion using MRgFUS for secondary generalized epilepsy due to subcortical lesion (NCT02804230). Another study plans to target the anterior thalamic nucleus to prevent secondary generalization in focal onset epilepsy patients (NCT03417297).

BRAIN TUMOR ABLATION

Stereotactic radiosurgery and conventional radiation therapy have been performed as an alternative or adjunct to open surgery in brain tumor patients. Radiation is associated with a long-term risk of adverse effect such as leukoencephalopathy

in the surrounding tissues of the target despite careful treatment planning to reduce radiation toxicity[75]. Thermal ablative therapy has been studied as another alternative to open surgery. MR-guided laser interstitial thermal therapy (LITT) is a novel stereotactic technique that ablates target tissue using a laser probe while monitoring the extent of thermal ablation using MR thermometry in real time. It has been applied to some selected epilepsies and malignant brain tumors as an alternative treatment, with promising initial results[9,59]. However, LITT still requires a skin incision and a small drill hole to insert the laser probe and can sometimes exacerbate mass effect by causing malignant peritumoral edema[9]. The first application of MRgFUS to brain tumor ablation was reported in 2010 in three patients with glioblastomas, however, at that time, the target temperature for achieving thermal coagulation (>55℃) could not be reached due to lack of specification of MRgFUS equipment and thus did not induce coagulative necrosis in the target[79]. With newer equipment in 2014, MRgFUS-mediated thermal ablation was tried in a patient with recurrent glioblastoma in the thalamic and subthalamic region with a volume of 6.5 mL[27]. Of the total 25 sonications applied by increasing the acoustic energy in a stepwise manner up to 19950 J per sonication, 17 sonications reached above 55℃ with a maximum peak temperature of 65℃. Preoperative contralateral hemiparesis improved from motor grade 3/5 to 4/5 after treatment without any adverse effect. Signal change in the sonicated tumor tissue was visible as bright zone in diffusion weighted images immediately after treatment. At 5 days postoperatively, non-enhancing areas were found in the sonicated tumor tissue on T1 weighted images with contrast, and this effect lasted over 21 days follow-up period. Clinical studies (NCT 00147056, NCT 01473485) are currently underway to verify the safety and efficacy of MRgFUS-mediated brain tumor ablation, with one study being pending to report (NCT01698437). MRgFUS tumor ablation has been limited to brain tumors deeper than 2.5 cm from the skull, because of the risk of significantly increasing the temperature of the scalp, skull and surrounding brain tissue when MRgHIFU ablation is applied to brain tumors near the skull. In the future, the feasibility of MRgFUS ablation in larger volume or high vascularity tumors should also be studied, as well as the role of MRgFUS ablation in tumor control as an independent or an adjuvant therapy for other treatment modalities.

PRECLINICAL STUDIES OF HIFU APPLICATION WITH NON-THERMAL MECHANISM

Sonothrombolysis

A preclinical study investigated the feasibility of MRgFUS-mediated thrombolysis of intracerebral hemorrhage (ICH)[85]. In a swine model of ICH, the authors demonstrated that implanted clots with a volume of 4 mL (n=5) were completely lysed by MRgFUS (parameters : 230 kHz, pulse repetition rate 1 kHz, duty cycle 10%, and sonication duration 30 seconds) that was performed after 3 hours of clot dwell time. Sonication at 750 W was applied in craniotomized pigs, whereas 1500 W was required in pigs with the skull intact. There was neither evidence of blood-brain barrier disruption nor necrosis caused by thermal injury in the adjacent normal brain. In cadaveric model of ICH, all clots with a mean ICH volume of 27 mL (n=4) were liquefied over 95% of each clot after transcranial MRgFUS (parameters : 230 kHz, power of 3950 W, sonication duration 30 seconds, 1 kHz pulse repetition rate, and 10% duty cycle), except for one ICH in which ultrasound energy could not reach its target due to interaction of the dissolved gas generated by the decay of specimen. The researchers also studied the feasibility of MRgFUS thrombolysis for intraventricular hemorrhage using a cadaveric model (n=1), reporting that significant volume of thrombus was lysed after a single sonication using the same parameters as described above.

Cerebrospinal fluid diversion

One study demonstrated the technical feasibility of noninvasive third ventriculostomy using MRgFUS in pigs. Inertial cavitation was generated, resulting in tissue fractionation, with higher peak rarefaction pressures than those used in thermal ablation[4]. Seven pigs underwent sonication at 650 kHz via craniectomy, while two underwent sonication (one at 650 kHz and another at 230 kHz) through an *ex vivo* human skull placed over the beam pathway after craniectomy was performed. Third ventriculostomy was successfully performed in 6 of 9 swine including one treated at 230 kHz through the skull. A small amount of subarachnoid hemorrhage was observed around the successful ventriculostomies, and in the animal treated transcranially at 650 kHz, microhemorrhage was identified at a site distal from the target. Therefore, in future studies, optimization of ultrasonic parameters

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Table 3. Preclinical research on MRgFUS-facilitated targeted drug delivery

Disease indication	Drug category	Therapeutic agent of interest	Subject/disease model	FUS parameters*	Results	Year
Brain tumor	Conventional chemotherapy	Lipo-Dox	Rat/gliosarcoma	1700; 1.2; 10; 1; 60–120, 5–9 sonications in total	↓ tumor growth ↑ survival	2012[116]
		IL-4 targeted Lipo-Dox	Mouse/GBM	1000; 0.7; _; 1: _, 5% duty cycle	↓ tumor growth ↑ survival	2012[124]
		Lipo-Dox	Rat/gliosarcoma	690; 0.55–0.81; 10; 1; 60, 5–20 sonications in total, 3 weekly treatments	↓tumor growth, ↑ survival	2013[8]
		Free Dox	Mouse/GBM	612.5; 0.4; 10; 1; 180	↓ tumor growth ↑ survival	2014[66]
		BCNU	Rat/GBM	400; 0.62; 10; 1; 30	↓ tumor growth ↑ survival	2010[73]
		TMZ	Rat/gliosarcoma	500; 0.6; 10; 1; 60	↓ tumor growth ↑ survival	2013[122]
	Monoclonal antibody	Anti-HER2 Ab (Herceptin)	Mouse/normal	690; 0.6 or 0.8;10; 1; 40	Targeted Ab delivery	2006[64]
		Anti-HER2 Ab (Herceptin)	Rat/metastatic breast cancer (HER2+)	690; 0.69; 10; 1; 60, 6 weekly treatments	↓ tumor size ↑ survival	2012[95]
	Nanoparticle	Epirubicin immobilized on MNP	Rat/GBM	400; 0.62; 1; 10; 1; 120	↓ tumor growth ↑ survival	2010[74]
		BCNU immobilized on MNP	Rat/GBM	400; 0.7; 10; 1; 30	↓ tumor growth	2010[23]
		Cisplatin immobilized on NP	Rat/gliosarcoma, GBM	1140; 0.6 or 0.8; _; _ ; 120, 0.5% duty cycle	↓ tumor growth ↑ survival	2017[114]
	Gene therapy	HSV1-tk-loaded VCMBs/ ganciclovir	Rat/GBM	1000; 0.7; _; 5; 120	↓ tumor growth ↑ survival	2017[18]
	Cells	NK-92 cells (chimeric HER2 antigen receptor+)	Rat/metastatic breast cancer (HER2+)	551.5; 0.33; 10; 1; 120	↑ NK-92 cell accumulation at the tumor sites	2013[2]
		NK-92 cells (chimeric HER2 antigen receptor+)	Rat/metastatic breast cancer (HER2+)	551.5; _; 10; 2; 120	↓ tumor growth and ↑ survival in the front-loaded treatment	2016[3]
AD	Antibody	Anti-Aβ Ab	Tg mouse/AD	690; 0.67–0.8; 10; 1; 40–45	↑ Ab delivery ↑ endogenous IgG	2008[98]
		Anti-Aβ Ab (BAM-10)	Tg mouse/AD	558; 0.3; 10; 1; 120	↓ Aβ plaques	2010[56]
	Nanoparticle	Anti-Aß Ab (6E10) immobilized on NP	Tg mouse/AD	2500; 0.95–2.21; _; _; 60	↑ Ab delivery	2014[125]
Parkinson's disease	Antibody	Anti-DRD4 Ab	Mouse/normal	690; 0.6-1.1; 10; 1; 40	↑ Ab delivery	2006[65]
	Drug	Lipo-rhFGF20	Rat/6-OHDA lesioned	690; _; 10; 1; 60, 3 W	↑ drug delivery ↓ motor dysfunction ↓ DA neuronal loss	2018[90]
Huntington's disease	Gene therapy	cc-siRNA-Htt	Rat/normal	558; 0.3; 10; 1; 120	↓ Htt expression	2012[13]
Unspecified	Gene therapy	AAV9-GFP	Mouse/normal	1180; 0.53–0.6; 10; 1; 120	Targeted GFP expression	2012[113]
		AAV2-GFP	Mouse/normal	1500; 0.44–0.7; 10; 1; 120	Targeted GFP expression	2013[46]

*Frequency (kHz); negative peak pressure (MPa); burst length (ms); repetition frequency (Hz); total US duration (sec). MRgHIFU : magnetic resonance-guided focused ultrasound, FUS : focused ultrasound, Lipo-Dox : liposomal doxorubicin, ↓ : inhibition/reduction, ↑ : increase, GBM : glioblastoma multiforme, _ : unspecified, BCNU : 1,3-Bis(2-chloroethyl)-1-nitrosourea, TMZ : temozolomide, HER2 : human epidermal growth factor receptor 2, Ab : antibody, MNP : magnetic nanoparticle, NP : nanoparticle, HSV1-tk : herpes simplex virus type 1-thymidine kinase, VCMB : VEGFR2-targeted and cationic microbubble, NK : natural killer, Aβ : amyloid-beta, AD : Alzheimer's disease, IgG : immunoglobulin G, DRD4 : dopamine receptor D4, rhFGF20 : recombinant human fibroblast growth factor-20, OHDA : hydroxydopamine, Tg : transgenic, DA : dopaminergic, cc-siRNA : cholesterol-conjugated small interfering RNA, Htt : Huntingtin protein, AAV : adeno-associated virus, GFP : green fluorescent protein

to improve the safety and efficacy of this procedure is of paramount importance.

CLINICAL APPLICATION OF PULSED FUS FOR BBB OPENING

The BBB is a major impediment to effective pharmaceutical treatment of a wide array of intracranial diseases[14,36]. Cerebral endothelial cells, which constitute the BBB, have several unique anatomical features which endow them with formidable barrier properties, that is, the presence of tight junctions between neighboring cells and remarkably fewer transport vesicles and fenestrations compared to other tissues. These attributes impede the paracellular and transcellular transports of molecules, respectively[14,30]. Moreover, the BBB expresses drug-efflux transporters such as P-glycoproteins that pump foreign substances out of the cells[7,36]. For these reasons, most systemically administered therapeutic agents, except nonpolar lipophilic small agents (<400 Da) that readily pass the BBB, are unable to cross the BBB to the levels sufficient to achieve therapeutic quantities[93,94]. Several attempts have been made to overcome this problem such as reducing the size or increasing the lipid solubility of therapeutic agents, transiently osmotically opening the BBB, or to administer agents intranasally in order to bypass the BBB. As part of this effort, MRgFUS has been explored for its BBB-opening effects[14]. Several preclinical studies have demonstrated that pulsed ultrasound can safely open the BBB with spatial and temporal specificity at selected ultrasound parameters, resulting in significant increase in drug concentration at the target site[50,51]. The extent of BBB opening depends on the size and concentration of intravenously delivered preformed microbubbles, as well as ultrasound parameters such as intensity and sonication time[14]. Simultaneously, precise targeting of BBB disruption can be estimated by regional contrast extravasation on the MR images which correlates with the amount of drug delivery[22,115]. FUS-mediated BBB opening is transient but lasts for approximately 4–6 hours after treatment, before the BBB closes again[78,80,104].

Brain tumors

Over the past decade, many preclinical studies on FUS-mediated BBB opening to enhance drug delivery and to improve the treatment efficacy for various intracranial diseases have

Table 4. Current status of clinical trials on pulsed LIFU application for BBB opening

Indication	Stage	Subtype	US treated region	Drug	End points	US Device/US parameters	Status
Brain tumor	Phase I/IIa	Recurrent GBM	Tumor	Carboplatin	Safety, feasibility of BBBD, PFS, OS	SonoCloud® (CarThera, Paris, France) 0.5–1.1 MPa	Recruiting (NCT02253212)
	Phase I	GBM	Resected surgical cavity	TMZ	Safety, feasibility of repeated BBBD	ExAblate® (InSightec, Tirat Carmel, Israel) 220 kHz	Not yet recruiting (NCT03551249, NCT03616860)
	Phase I	Unspecified	Tumor	Doxorubicin	Safety, feasibility of BBBD	ExAblate® (InSightec) 220 kHz	Recruiting (NCT02343991)
Neurodegenerative disease	Phase I	Mild to moderate PDD	Right parieto-occipito-temporal lobes	No	Safety, feasibility of BBBD	ExAblate® (InSightec) 220 kHz	Recruiting (NCT03608553)
	Phase I	Mild AD	Frontal lobes	No	Safety, feasibility of BBBD, Δ Aβ plaques	ExAblate® (InSightec) 220 kHz 4.6 W for stage 1 4.5 W for stage 2	Completed and published[71] (NCT02986932)
	Phase I/II	Mild AD	Left supramarginal gyrus	No	Δ glucose metabolism, safety of BBBD	SonoCloud® (CarThera) unspecified	Recruiting (NCT03119961)
	Phase I	ALS	Primary motor cortex	No	Safety, feasibility of BBBD	ExAblate® (InSightec) unspecified	Recruiting (NCT03321487)

LIFU : low-intensity focused ultrasound, BBB : blood-brain barrier, US : ultrasound, GBM : glioblastoma multiforme, BBBD : blood-brain barrier disruption, PFS : progression-free survival, OS : overall survival, TMZ : temozolomide, PDD : Parkinson's disease with dementia, AD : Alzheimer's disease, Δ : change in, Aβ : amyloid-β, ALS : amyotrophic lateral sclerosis

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been conducted. Several animal studies have taken place including : targeted therapies of malignant gliomas and metastatic brain tumors using various types of therapeutic agents including monoclonal antibodies (e.g., trastuzumab for HER 2-positive breast cancer brain metastasis), gene therapy agents, and immune cells as well as conventional chemotherapeutic agents including doxorubicin and temozolomide. These studies consistently showed enhanced drug delivery into tumors, which led to inhibition of tumor growth as well as improved survival (Table 3). Though ultrasound parameters varied in the literature, the acoustic negative peak pressure generally ranged between 0.3–1.0 MPa, and as pressure increased beyond 0.8 MPa, erythrocyte extravasation was observed more frequently[18,64]. These promising preclinical results have promoted translation to clinical application of FUS-mediated BBB opening and enhanced drug delivery to the brain, with several phase I or I/IIa clinical trials for malignant brain tumors underway (NCT02253212, NCT03551249, NCT03616860, NCT02343991) (Table 4). Carpentier et al.[17] have recently reported the interim results of a clinical trial on the safety of ultrasound dose-escalation ranging from 0.5 to 1.1 MPa using SonoCloud® (CarThera, Paris, France), an implantable pulsed ultrasound system in the recurrent glioblastoma patients. The authors demonstrated that repeated monthly BBB opening was safe up to 1.1 MPa, with the extent of BBB opening being most effective with acoustic pressures of ≥0.8 MPa (NCT02253212).

Neurodegenerative diseases

FUS is being examined for its potential role in neurodegenerative diseases including Alzheimer's disease (AD), PD, and Huntington's disease (HD). In 2008, Raymond et al.[98] reported that using a transgenic mouse model of AD, FUS-mediated BBB opening increased anti-amyloid beta (Aβ) antibodies bound to Aβ plaques 2.7-fold in targeted areas. Another study using a transgenic mouse model of AD also demonstrated enhanced delivery of anti-Aβ monoclonal antibody (BAM-10) following MRgFUS application and significant reduction in Aβ plaques number and size (both 12%) as well as the surface area covered by Aβ plaques (23%) in the FUS-treated areas[56]. These results were seen in 4 days with only one treatment. Surprisingly, FUS-mediated BBB opening alone has also proven to induce significant Aβ plaque reduction[12,57,69]. Studies showed that endogenous immunoglobulins (IgG and IgM), which were present in the blood circulation, entered the brain after FUS-mediated BBB opening and bound to Aβ plaques, leading to activation of the innate immune system against pathologic proteins. Through such mechanism, FUS seems to assist in clearing Aβ plaques even without externally-administered antibodies. Also, activation of astrocytes and microglia was found, as well as increased internalization of Aβ within these cells following FUS treatment[57]. After a single treatment with FUS alone, Aβ plaque size and total surface area decreased significantly by 20% and 13%, respectively, and Aβ plaque number trended to decrease by 9%, which were comparable to the results of previous studies of FUS treatment with antibodies[56,57]. In addition, and even more surprisingly, sonication was reported to increase neurogenesis in the hippocampus[12,101]. Scarcelli et al.[101] demonstrated that pulsed LIFU combined with microbubbles applied at typical parameters for BBB opening (10 ms bursts, 1 Hz pulse repetition frequency, mean peak pressures of 0.96 MPa, and duration of 120 seconds) is able to stimulate neurogenesis (228% increase) in the dentate gyrus of the hippocampus of adult mice. Another study by the same group also verified the ability of inducing neurogenesis of pulsed LIFU. The authors applied MRgFUS (10 ms bursts, 1 Hz pulse repetition frequency, mean peak pressure of 1.18 MPa, and duration of 120 seconds) targeting the dorsal hippocampus with microbubbles using transgenic mouse model of AD and demonstrated that the number of newborn neurons in the dentate gyrus of the hippocampus significantly increased by 252% after 4 weekly ultrasound treatment[12]. Also, total dendrite length (323%) and branching were significantly greater in the ultrasound treated animals compared with untreated controls. Along with significant decrease in the Aβ plaque burden (size, number, and the surface area loaded by Aβ by 20%, 29%, and 19%, respectively) in the hippocampus after MRgFUS treatment, the neuronal proliferation and maturation in the dentate gyrus was correlated with spatial memory improvement. The mechanism by which FUS mediates the hippocampal neurogenesis at the BBB opening parameter has not yet been established. One potential mechanism may be illustrated with mechanical bioeffect of pulsed LIFU on stimulation of neurons, which is accompanied by activation of cellular molecular signaling cascade and in turn upregulation of trophic cytokine such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor which are essential for promoting hippocampal neurogenesis[12,16,99,101,117]. Tufail et al.[117] reported that pulsed LIFU

(0.35 MHz, 50 cycles per pulse, 1.5 kHz pulse repetition frequencies, 500 pulses) without microbubble contrast agents targeted on the hippocampus of mouse significantly increased the density of BDNF in CA1 (148%) and CA3 regions (158%) of the hippocampus. Although the ultrasound parameters to elicit neuromodulatory effects are typically different from those for BBB opening, these observations suggest that pulsed LIFU may promote neurogenesis through a similar mechanism, even at BBB opening parameters, though further confirmatory studies are needed. Another potential mechanism might be explained as activation of PI3K-Akt-mTOR signaling pathway, which promotes cellular survival and growth, in response to FUS-mediated BBB opening[12]. Indeed, activation of PI3K-Akt-mTOR signaling leads to improve survival of newborn neurons in the dentate gyrus in the adult mouse model of AD, rescuing newborn neurons from Aβ-induced dendritic growth deficits[70]. Jalali et al.[53] demonstrated that ultrasound-mediated BBB opening combined with microbubbles in rats induced activation of PI3K-Akt signaling pathway in the neurons. Taken together, these findings suggest that FUS-mediated BBB opening has interesting potential as a therapeutic strategy for AD treatment. Recently, the results of a phase I safety and feasibility trial for FUS-mediated BBB opening in mild AD patients have been published (NCT02986932)[72]. In conjunction with intravenous microbubble contrast, MRgFUS was applied to a small volume of white matter in the frontal lobe in five patients. In all patients, BBB opening was successful without serious adverse events, but without any evidence of amyloid clearance as measured by positron emission tomography. Another phase I/II trial of BBB opening in mild AD patients is being underway (NCT03119961) (Table 4). For other neurodegenerative diseases such as PD and HD, preclinical and clinical trials are underway (Tables 3 and 4). Burgess et al. studied the feasibility of MRgFUS-facilitated non-invasive gene therapy to silence the mutant Huntingtin (Htt) gene that results in expression of abnormal Htt protein causing progressive neuronal damage in HD[13]. Decrease in Htt protein expression had proven to correlate with improved motor function and neuronal survival in the mouse model of HD, however, cholesterol-conjugated small interfering RNA against Htt (cc-siRNA-Htt), which reverses pathology, was injected into the striatum in an invasive manner in the previous study[31]. Instead, Burgess et al.[13] used MRgFUS to enhance the delivery of intravenously administered cc-siRNA-Htt into the striatum and demonstrated significant Htt knockdown. These results suggest that MRgFUS-mediated gene therapy could be a promising therapeutic approach for genetic neurological disorders.

SUMMARY

MRgFUS is an emerging technique allowing non-invasive, incision-free transcranial treatment for a variety of intracranial diseases via thermal and non-thermal mechanisms. Accurate thermal ablation via MRgHIFU-mediated stereotactic lesioning can be confirmed with real-time visualization of the target volume with MRI thermometry. In ET and PD patients, MRgHIFU is being performed unilaterally due to concern over the high incidence of adverse effects associated with bilateral lesions[5], and clinical studies are ongoing to assess its long-term safety and efficacy. In addition, emerging preclinical evidence suggests that MRgFUS-mediated BBB opening has potential to revolutionize the targeted treatment of selected brain diseases, including brain tumors and neurogenerative disease. Lots of work is needed to establish safe and effective ultrasound parameters before routinely applying MRgFUS-mediated BBB opening to humans. As such, several phase 1 clinical trials are being conducted by research institutes worldwide. We are now seeing the advent of a new era in the treatment of brain diseases.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

This type of study does not require informed consent.

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