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Therapeutic Potential of Transcranial Focused Ultrasound for Rett Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Rett syndrome (RTT) is a severe neurodevelopmental disorder occurring almost exclusively in females and is caused by loss-of-function mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2) in the majority of cases. MeCP2 is essential for the normal function of nerve cells, including neuronal development, maturation, and synaptic activity. RTT is characterized by normal early development followed by autistic-like features, slowed brain and head growth, gait abnormalities, seizures, breathing irregularities, and cognitive disabilities. Medical management in RTT remains supportive and symptomatic. Brain-derived neurotrophic factor (BDNF) has been implicated in the pathophysiology of RTT. Recent studies have shown a phenotypic reversal by increasing BDNF expression in a RTT mouse model. Thus, manipulation of BDNF expression/signaling in the brain could be therapeutic for this disease. Transcranial focused ultrasound for (tFUS) can noninvasively focally modulate human cortical function, stimulate neurogenesis, and increase BDNF in animal studies. Consequently, tFUS may be of therapeutic potential for Rett syndrome. Further evaluation of the therapeutic effects of tFUS in *Mecp2* deficient animal models is needed before clinical trials can begin.

MeSH Keywords: **Brain-Derived Neurotrophic Factor • Methyl-CpG-Binding Protein 2 • Neurogenesis • Rett Syndrome • Ultrasonography, Interventional**

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Background

Rett syndrome (RTT) is a neurodevelopmental disorder that affects female children almost exclusively. RTT is the leading cause of severe intellectual disability in females, and is estimated to affect one in every 10,000 to 15,000 live female births in all ethnic groups worldwide. After 6 to 18 months of apparently normal early growth, RTT patients show global deceleration of psychomotor development and subsequent loss of acquired cognitive and motor skills. Children with RTT often exhibit autistic-like behaviours in the early stages and have slowed brain and head growth, problems with walking, seizures, and breathing irregularities [1,2]. The course of RTT varies from child to child, and children with RTT who survive into adulthood have severe mental retardation and require intensive support [3].

Nearly all RTT cases are caused by a mutation in the gene encoding the transcriptional regulator methyl-CpG-binding protein 2 (MeCP2), located on the X chromosome [4]. The MeCP2 protein is present in cells throughout the body, although it is particularly abundant in brain cells. Initially MeCP2 was recognized as a transcriptional repressor/activator and, recently, it was also found to be involved in gene regulation at the post-transcriptional level [5–7]. Many of the genes that are known to be regulated by the MeCP2 protein are critical for the development and maturation of brain. Although mutations in the *MECP2* gene have been found to cause RTT, the specific functions of MeCP2 that are impaired by mutations and are responsible for RTT symptomatology remain unclear [8].

To date, no successful curative treatment has been established for RTT; treatment for the disorder is symptomatic. Medication may be needed for breathing irregularities, and anticonvulsant drugs may be needed to control seizures [8]. Therapy programs for RTT patients should include the use of assistive technology and rehabilitation interventions to reverse physical impairments [9].

In recent years, some preliminary trials of theoretically potential agents have been proposed [10]. For example, the pleiotropic growth factor insulin-like growth factor-1 (IGF-1) has been suggested as a therapeutic treatment for RTT patients. IGF-1 crosses the blood-brain barrier (BBB) and stimulates proliferation of neural progenitors, neuronal survival, neurite outgrowth, and synapse formation [11]. A recent study demonstrated that systemic treatment of *Mecp2* mutant mice with an active tripeptide fragment of IGF-1 extended the life span of the mice, improved locomotor functions, ameliorated breathing patterns, and reduced irregularities in heart rates [12].

Here, I propose that transcranial focused ultrasound (tFUS), a novel noninvasive brain stimulation technique, could be a potential treatment for RTT by improving several key features of RTT.

Medical Hypothesis

Brain-derived neurotrophic factor (BDNF) deregulation in Rett syndrome

BDNF is a member of the neurotrophin family of growth factors that have essential roles in neuronal survival and differentiation, and is a strong modulator of synaptic transmission and plasticity in the brain. In 2003, *Bdnf* gene was first identified as a possible neuronal target gene for MeCP2 [13]. Later it was found that BDNF protein levels in the whole-brain lysate in *Mecp2* knockout mice were decreased to about 70% of the wild-type level [14]. Lower *BDNF* mRNA levels were also found in autopsy brain samples from RTT subjects, which is similar to that found in *Mecp2* mutant mice [15,16]. Animal study demonstrated that deletion of *Bdnf* in *Mecp2* mutants caused an earlier onset of RTT-like symptoms, whereas increased brain BDNF expression in the *Mecp2* mutant extended the lifespan, rescued a locomotor defect, and reversed an electrophysiological deficit [14]. These findings suggested that RTT pathogenesis may be partially mediated through BDNF signalling, and therefore improving BDNF expression and/or signaling in brain could be therapeutic for this disease [14]. Since the administration of BDNF is not a useful clinical approach due to its low BBB penetration, medications that can increase endogenous BDNF expression or its downstream signaling pathways are more practical for the treatment of RTT [8,10].

Irregular breathing is one of the most typical symptoms of RTT. Common issues are hyperventilation, apnea, breath holding, and air swallowing that occurs generally while awake. Evidence from previous studies suggested BDNF signaling plays an important role in the respiratory pathophysiology of RTT [17,18]. A recent study using 7,8-dihydroxyflavone (7,8-DHF), a small molecule reported to activate the high affinity BDNF receptor (TrkB) in the brain, demonstrated delayed body weight loss, increased neuronal nuclei size, and improvement in breathing pattern irregularities in *Mecp2* mutant mice [19]. Another study by Schmid et al. [20] reported LM22A-4, a small molecule TrkB agonist, could increase TrkB activation and improve respiratory function in heterozygous female *Mecp2* mutant mice.

Transcranial focused ultrasound

Ultrasound, also called sonography, is safe and creates images of the inside of the body using sound waves. Most ultrasounds are done using a transducer on the surface of the body. Advancements in ultrasound technology may permit physicians to get a better diagnostic image by inserting a special

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transducer into one of the body's natural openings [21–23]. The new ultrasound modality tFUS delivers highly focused acoustic energy to a small region of the brain in a noninvasive manner. Recently tFUS has been investigated as a new mode of noninvasive brain stimulation, which offers high spatial resolution and depth control. In addition, tFUS has been used for targeted drug delivery by reversible BBB disruption [24]. Recently, tFUS, with its ability to deliver highly focused acoustic energy to a small region of the brain in a noninvasive manner, is gaining attention as a new mode of brain stimulation [25,26]. Some preliminary studies suggest that tFUS could be used for the treatment of patients with neuropathic pain, essential tremor, Parkinson's disease, Alzheimer's disease, or major depression [26–29]. It could be a potential strategy for the treatment of RTT for several reasons. Firstly, tFUS at low intensities has demonstrated the potential to increase growth factors, including BDNF [30]. A previous study demonstrated that *Mecp2* mutants could be rescued by application of exogenous BDNF [31]. Furthermore, *Bdnf* overexpression in embryonic day-18 hippocampal neurons prevents dendritic atrophy caused by *Mecp2* mutations [32]. These findings suggest that the brain BDNF level is decreased in RTT, and therapeutic approaches aimed at increasing BDNF levels may be able to counteract the effects of mutant *Mecp2*. Recently, Tufail et al. [30] demonstrated that hippocampal BDNF protein levels were increased following transcranial stimulation by tFUS in mice. Similarly, Yang et al. [33] reported that low-intensity pulsed ultrasound stimulation in rat brain astrocytes is capable of increasing neurotrophic protein levels, including BDNF.

Secondly, hippocampal neurogenesis is central to learning and memory. A study using a human neuroblastoma cell line carrying a partially silenced *MECP2* gene found that *MECP2* inactivation affected the cell fate of neural progenitors and/or neuronal differentiation and maintenance [34]. In a recent study, Hao et al. [35] demonstrated that forniceal deep brain stimulation can restore *in vivo* hippocampal long-term potentiation and hippocampal neurogenesis in RTT mice. In adult mice, tFUS significantly increased the number of proliferating cells and newborn neurons in the hippocampus [36]. This provides further evidence that tFUS can stimulate hippocampal neurogenesis, a process involved in learning and memory and affected in RTT.

Evaluation of the Hypothesis

The use of tFUS in RTT deserves a thorough examination. I present several recommendations for applying this hypothesis of RTT treatment with tFUS. Firstly, the discovery of the main RTT gene, *MECP2*, enabling several mouse models of RTT based on *Mecp2* dysfunction, and allowed testing of the potential therapeutic effect of tFUS in RTT subjects [3738]. Furthermore, induced pluripotent stem cells (iPSCs) reprogrammed from skin fibroblasts of RTT individuals have been successfully differentiated into neurons [39]. RTT patient iPSC-derived neurons have shown changes in soma size, information encoding properties, and synaptic connectivity that are defective in RTT [39]. The therapeutic potential of tFUS in RTT subjects could thus be tested in this iPSC model of RTT. Second, any promising results in animal or iPSC model studies, suggest the need for further double-blind, placebo-controlled randomized studies to confirm that tFUS has therapeutic effects in RTT patients. The beneficial effects of tFUS in the brain seem to be related to timing and dose. The optimal tFUS parameters for RTT treatment await further exploration. Finally, all safety concerns should be evaluated in preclinical and clinical studies during tFUS treatment of RTT patients.

Conclusions

Currently, tFUS, a noninvasive brain stimulation, is being used experimentally to enhance brain plasticity and recovery of function through increasing BDNF levels and neurogenesis. The tFUS methodology may offer protection to the neurological systems and improve the respiratory and cognitive function of patients with RTT. Obviously, further experimental studies and clinical trials are needed in order to confirm the therapeutic potential of tFUS in RTT patients.

Declaration of interest

None.

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