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Research Article

# Transcranial focused ultrasound stimulation reduces vasogenic edema after middle cerebral artery occlusion in mice

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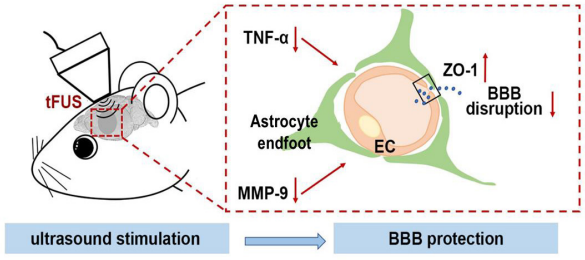
Li-Dong Deng[1], Lin Qi[1], Qian Suo[1], Sheng-Ju Wu[1], Muyassar Mamtilahun[1], Ru-Bing Shi[1], Ze Liu[1], Jun-Feng Sun[1], Yao-Hui Tang[1], Zhi-Jun Zhang[1], Guo-Yuan Yang[1, 2, *], Ji-Xian Wang[1, *]

## From the Contents



**Graphical Abstract** *Transcranial focused ultrasound stimulation protects the blood-brain barrier after middle cerebral artery occlusion in mice*




## Abstract

Blood-brain barrier (BBB) disruption underlies the vasogenic edema and neuronal cell death induced by acute ischemic stroke. Reducing this disruption has therapeutic potential. Transcranial focused ultrasound stimulation has shown neuromodulatory and neuroprotective effects in various brain diseases including ischemic stroke. Ultrasound stimulation can reduce inflammation and promote angiogenesis and neural circuit remodeling. However, its effect on the BBB in the acute phase of ischemic stroke is unknown. In this study of mice subjected to middle cerebral artery occlusion for 90 minutes, low-intensity low-frequency (0.5 MHz) transcranial focused ultrasound stimulation was applied 2, 4, and 8 hours after occlusion. Ultrasound stimulation reduced edema volume, improved neurobehavioral outcomes, improved BBB integrity (enhanced tight junction protein ZO-1 expression and reduced IgG leakage), and reduced secretion of the inflammatory factors tumor necrosis factor-α and activation of matrix metalloproteinase-9 in the ischemic brain. Our results show that low-intensity ultrasound stimulation attenuated BBB disruption and edema formation, which suggests it may have therapeutic use in ischemic brain disease as a protector of BBB integrity.

**Key Words:** blood-brain barrier; brain edema; cerebral blood flow; ischemia; matrix metalloproteinase-9; neurobehavioral outcomes; tight junction; transcranial ultrasound

## Introduction

Stroke, including ischemic and hemorrhagic types, is the second leading cause of death worldwide and has a high risk of disability, of which ischemic stroke accounts for approximately 76% (Campbell et al., 2019; Zhong et al., 2020; Virani et al., 2021). Tissue plasminogen activator is the only FDA-approved medication for ischemic stroke but is limited by a short therapeutic window and has a high risk of hemorrhage (Miller et al., 2011; Liu et al., 2016). Other therapeutic approaches are necessary, including ones that can attenuate ischemic brain injury.

One of the pathological phenomena that occurs during ischemic stroke is blood-brain barrier (BBB) dysfunction (Li et al., 2019; Alamri et al., 2021). The BBB consists of endothelial cells, pericytes, astrocytic end-foot processes, the basement membrane, and tight junctions (Pan et al., 2020). It separates the central nervous system (CNS) from the blood circulation, maintaining a microenvironment appropriate for neurons and glial functioning. When ischemic stroke occurs, BBB disruption occurs and cytotoxic edema develops, which leads to infiltration of hematogenous fluid from the blood circulation into the brain via disrupted tight junctions (vasogenic edema), as well as regional neuroinflammation (Obermeier et al., 2013; Zhang et al., 2020). To date, several potential therapeutic approaches have been developed to attenuate BBB disruption (Abdulkadir et al., 2020). In animal studies, researchers have discovered drugs that reduce hyperpermeability by inhibiting inflammatory mediators, decreasing matrix metalloproteinases (MMPs), and increasing angiopoetin-1 to enhance tight junctions (Jiang et al., 2018; Zhang et al., 2020). MMP-9 is a gelatinase found in blood and microvessel wells that can cause degradation of tight junction proteins during ischemic brain injury. Inhibiting hyperexpression of MMP-9 might attenuate BBB disruption (Qi et al., 2016). However, such a treatment would be difficult in clinical practice because of the narrow therapeutic time window and safety issues.

[1]Department of Rehabilitation Medicine, Ruijin Hospital, School of Medicine, and Med-X Research Institute and School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China; [2]Department of Neurology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
*Correspondence to: Guo-Yuan Yang, MD, PhD, gyyang0626@163.com; Ji-Xian Wang, MD, PhD, wangjixian6@163.com.
https://orcid.org/0000-0003-4194-8175 (Guo-Yuan Yang); https://orcid.org/0000-0002-3660-3175 (Ji-Xian Wang)

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