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Invited review

Noninvasive and targeted delivery of therapeutics to the brain using focused ultrasound

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ABSTRACT

The range of therapeutic treatment options for central nervous system (CNS) diseases is greatly limited by the blood-brain barrier (BBB). While a variety of strategies to circumvent the blood-brain barrier for drug delivery have been investigated, little clinical success has been achieved. Focused ultrasound (FUS) is a unique approach whereby the transcranial application of acoustic energy to targeted brain areas causes a noninvasive, safe, transient, and targeted opening of the BBB, providing an avenue for the delivery of therapeutic agents from the systemic circulation into the brain. There is a great need for viable treatment strategies for CNS diseases, and we believe that the preclinical success of this technique should encourage a rapid movement towards clinical testing. In this review, we address the versatile applications of FUS-mediated BBB opening, the safety profile of the technique, and the physical and biological mechanisms that drive this process.

This article is part of the Special Issue entitled “Beyond small molecules for neurological disorders”.

Contents

Abbreviations: AAV, adeno-associated virus; Aβ, amyloid beta; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BBB, blood-brain barrier; BBBO, blood-brain barrier opening; BCNU, *bis*-chloroethylnitrosourea; BDNF, brain-derived neurotrophic factor; BOLD, blood-oxygen-level dependent; BrdU, bromodeoxyuridine; CNS, central nervous system; CSF, cerebrospinal fluid; DCE, dynamic contrast enhanced; DCX, doublecortin; DMSO, dimethyl sulfoxide; EC, endothelial cell; *f*, frequency; FDA, Food and Drug Administration; FUS, focused ultrasound; GABA, γ-aminobutyric acid; GFAP, glial fibrillary acidic protein; GFP, green fluorescent protein; GSK3β, glycogen synthase kinase 3 beta; Her2, human epidermal growth factor receptor 2; HIFU, high-intensity focused ultrasound; HRP, horseradish peroxidase; Htt, huntingtin protein; IBA1, ionized calcium-binding adapter molecule 1; IL-12, interleukin-12; K_{trans}, transfer coefficient; MB, microbubble; MI, mechanical index; microSPECT, micro-Single Photon Emission Computed Tomography; MRI, magnetic resonance imaging; MS, multiple sclerosis; NeuN, neuronal specific nuclear protein; PD, Parkinson's disease; PNP, peak negative pressure; RBC, red blood cell; SDS, sodium dodecyl sulfate; SSEP, suppressed somatosensory evoked potential; $t_{1/2}$, half closure time; TJ, tight junction; VAF, vanadium acid fuchsin; VEGF, vascular endothelial growth factor; ZO, zonula occludens.

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1. Structure and function of the blood-brain barrier

Proper cerebral function is dependent upon a tightly regulated extracellular milieu surrounding neurons and glia (De Bock et al., 2013). The blood-brain barrier (BBB) plays a major role in maintaining this environment by selectively isolating the parenchyma from the circulatory system. The major anatomical features of the BBB include a layer of specialized endothelial cells (ECs), a basement membrane, and a non-continuous layer of pericytes, which is surrounded by another basement membrane. An additional layer, composed of astrocytic endfeet, surrounds the second basement membrane (Hawkins and Davis, 2005) (Fig. 1). At the interface of adjacent ECs are adherens and tight junction (TJ) complexes, consisting of transmembrane proteins, which include various junctional adhesion molecules, claudins, and occludens. The intracellular domains of these proteins are anchored to the cytoskeleton of ECs, while the extracellular domains form homodimers with proteins on adjacent ECs (Abbott et al., 2006). Together, these bonds create a tight link between ECs, contributing to a 'physical barrier' which limits paracellular diffusion to small (<400–500 Da), water soluble molecules (Pardridge, 2005).

While small gaseous or lipophilic molecules can freely diffuse through the lipid membrane of ECs, the presence of specific transporter complexes in the luminal and abluminal surfaces strictly regulate the transcellular movement of larger polar and non-polar molecules (Abbott et al., 2006). These complexes contribute to a 'transport barrier' which facilitates the movement of select substances, such as glucose and essential amino acids, transported by specific carrier proteins (Abbott et al., 2006). Vascular ECs in the central nervous system (CNS) also make use of receptor-mediated transcytosis and adsorptive transcytosis to regulate the movement of large molecules. However, these cells have a much lower degree of endocytosis than in peripheral endothelia (Pardridge, 2002). While fewer fenestrations and vesicles result in reduced transcytosis, efflux pumps (e.g. *P*-glycoprotein and multidrug resistance-associated protein) and enzymes prevent toxic molecules from accumulating (Abbott et al., 2006).

Together, the unique combination of features that make up the BBB act to maintain homeostasis and protect the brain from infection. Its importance is exemplified by several neurodegenerative diseases where aberrant BBB function has been observed. In humans, a variant of the *APOE* gene is strongly associated with

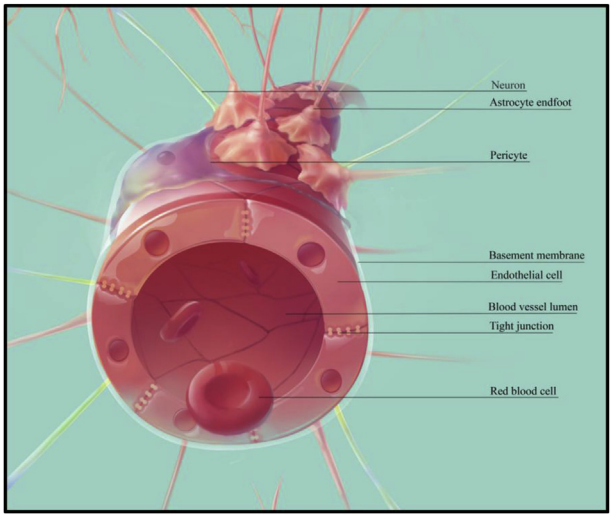

Fig. 1. Components of the BBB. The BBB is composed of a layer of specialized vascular ECs, linked together by adherens and TJ proteins. This layer is surrounded by a basement membrane, then a non-continuous layer of pericytes. An additional basement membrane and astrocytic endfeet complete the major anatomical features of the BBB. This configuration contributes to the selective exclusion of a vast majority of therapeutic agents in circulation from entering the brain parenchyma. Abbreviations: BBB = blood-brain barrier, EC = endothelial cell, TJ = tight junction.