Blood-Brain Barrier Opening

Background Information

The blood-brain barrier (BBB) is a protective layer of tightly joined cells that lines the blood vessels in the brain and prevents harmful substances, such as toxins and infectious agents, from diffusing into the surrounding brain tissue. Unfortunately, it also limits the amount of medication that can reach diseased brain targets. Safely and temporarily opening this barrier to deliver drugs in therapeutic concentrations to the brain is a long-sought goal for treating a wide range of neurologic conditions, including brain tumors, Alzheimer's disease and epilepsy.

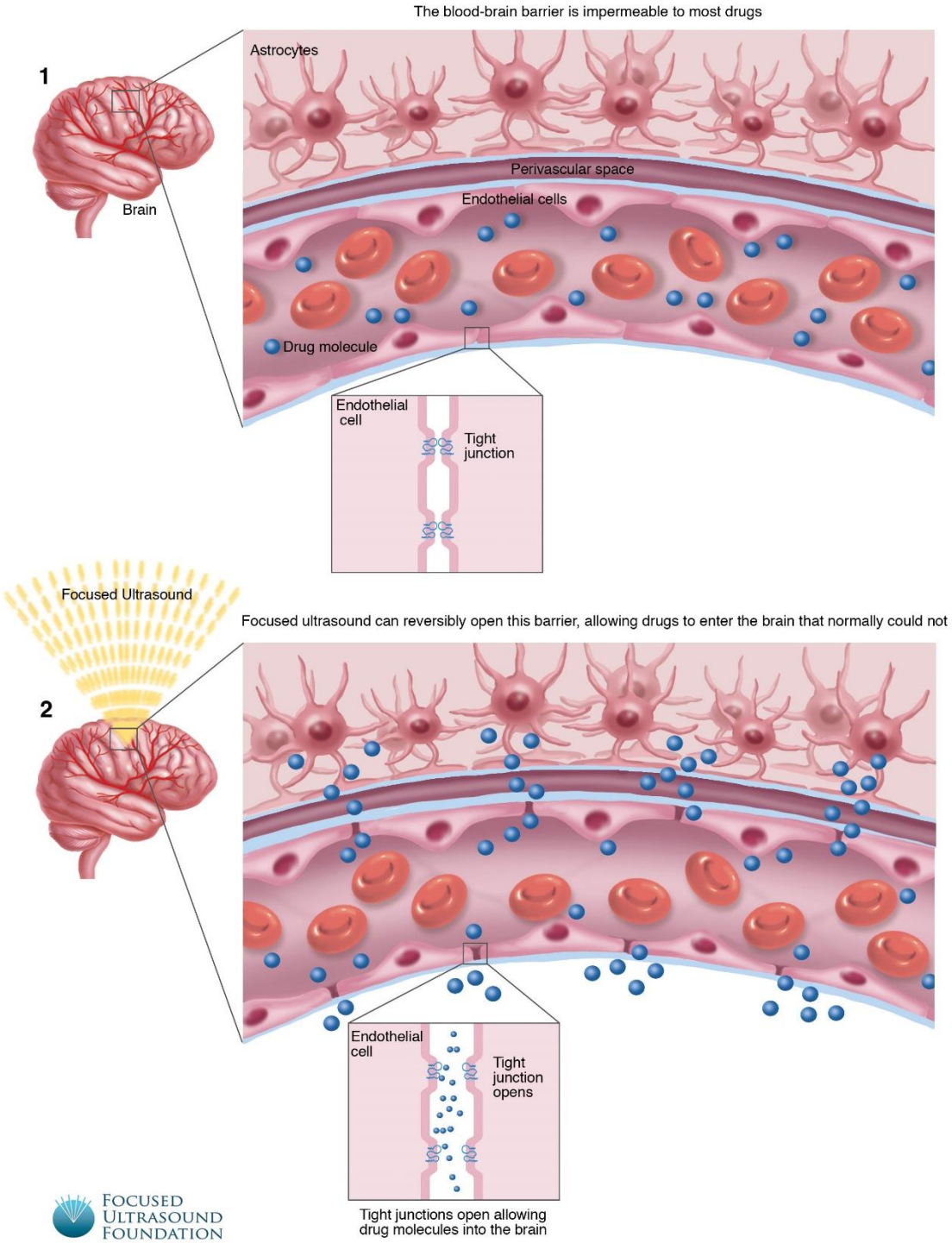
To date, several methods have been developed to circumvent or disrupt this barrier.[1] Hyperosmotic agents have been used to force water out of the endothelial cells, leading to cell shrinkage and disruption of the tight junctions between cells.[2] This treatment has a therapeutic window of several hours,[3] and one study found a 10-fold increase in the concentration of chemotherapy in the brain after hyperosmotic treatment.[4] However, there are concerns that since this treatment is non-specific it may cause systemic central nervous system toxicity.[5] Bradykinin, a vasodilator, has also been used to increase endothelium permeability, however the therapeutic window for this treatment is very short with permeability peaking at 15 minutes after treatment.[6] Convection-enhanced delivery is a more invasive option that uses a surgically implanted catheter to deliver drugs directly to the targeted region.[7] Additionally, both radiation therapy[8] and focused ultrasound (FUS)[9] have been shown to disrupt the BBB in a non-invasive, targeted manner. However, radiation has a highly variable therapeutic window and has inherent risks for toxicity. Focused ultrasound on the other hand has been able to safely and reliably produce a therapeutic window of up to four hours immediately after treatment.[10,11]

The mechanical effects of focused ultrasound, namely cavitation, are thought to be the principle cause behind this BBB disruption. Oscillating microbubbles in the vessels put pressure on the endothelium and force apart the tight junctions.[10,12] Large amounts of energy are needed for FUS to induce cavitation on its own, and using such high energies can lead to many of the negative side effects seen in previous research. Instead, recent work has investigated coupling focused ultrasound with ultrasound contrast agents – also known as microbubbles. Injecting these pre-formed bubbles prior to FUS treatment reduces the energy needed to disrupt the barrier since the ultrasound no longer needs to generate the bubbles on its own. When this technique was compared to thermal ablation, it was found to use up to two orders of magnitude less energy,[13] which results in a reduced risk of unintended tissue damage.[14]

This method of BBB disruption – FUS with microbubbles – has had very promising results. Normally only small molecules (typically smaller than 400 Da) with the proper charge and hydrophilicity can cross the BBB, but disruption of this barrier with FUS has been shown to enable molecules as large as 150 kDa to cross.[15–17]

Temporary opening of the blood-brain barrier in a safe and targeted manner with focused ultrasound unlocks a vast array of potential treatments. Immunotherapies such as IL-12 or even entire immune cells, as well as chemotherapeutics, can be delivered to notoriously difficult to treat brain tumors with this technique.[18–20] Various therapeutic drugs and molecules can be delivered for the treatment of depression,[21] Parkinson's disease,[22] and Huntington's disease[23] among many other neurological disorders. Even just opening the BBB may have therapeutic value for Alzheimer's disease by reducing the amyloid plaque burden.[24,25] Positive results from the first-in-human, feasibility and safety study for BBB opening with focused ultrasound at Sunnybrook Health Sciences Centre in Toronto could pave the way for translating all of these indications to the clinic in the near future.

Figure 1. Opening up the Blood-Brain Barrier to Deliver Drugs



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