



## **A REVIEW ARTICLE ON THE ULTRA SOUND MEDIATED DRUG DELIVERY SYSTEM**

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### **ABSTRACT**

*The delivery of the therapeutics Molecules (Drug molecules, Antibody growth factor, Nano-medicine formulation) to the central nervous system the blood brain barrier is the major barrier. When drug molecules are combined in the ultra sound can easily permeate in blood vessel of the brain known as the Sonoporation. By this method the therapeutics molecule easily penetrate in the brain and gives their effect. Here we described the principle of the ultrasound permeation, factor affecting , future out-look for the diagnosis and treatment of the various brain disorder.*

**KEYWORDS:** *Ultra sound, Blood brain barrier ,Sonoporation.*

### **INTRODUCTION**

The major challenges in the pharmaceutical research is that efficient delivery of the efficient therapeutics molecules in the brain due to the blood Brain barrier. The BBB restrict the permeation of the therapeutics molecules to the penetrate in the brain. BBB consist of the endothelial cell linked together by very tight junctions a thick basement membrane and layer of Astrocytes neurons and Pericytes. Which are only allowed the uptake of only small lipophilic drug, while preventing the vast majority of the drug molecules from entering to the CNS.(2)

Now a days there is the many updated approaches which used to overcomes BBB which leads to permeate the drug molecules to penetrate in the brain. The ultra sound mediated drug delivery system is the one of the best safe approaches to over comes the BBB. Its takes many attention for the opening of the BBB and improving the drug delivery.(3)

### **BLOOD BRAIN BARRIER**

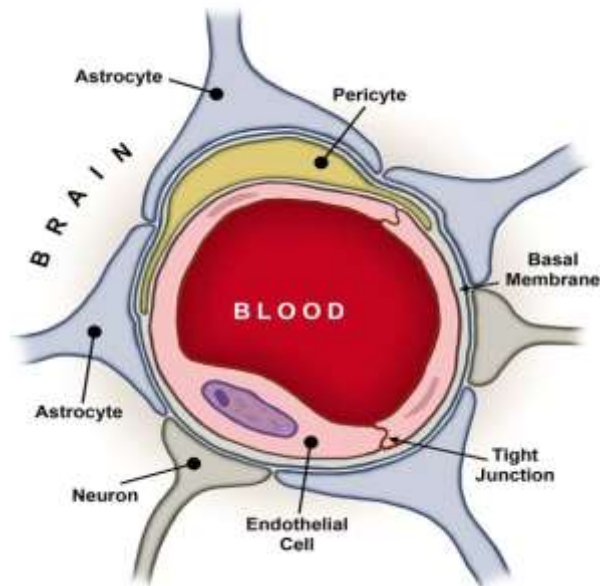
Blood-brain barrier discovery and existence has progressed over the years. It was first described by Ehrlich in 1885; he describe how dye injection into the blood circulation stained peripheral organs but not the spinal cord and the brain. Later in 1913, Edwin Gold mann showed that direct injection of trypan blue into the CSF stained cells within the CNS and not in the periphery. Reese and Karnovsky presented a solute exchange barrier between the blood and the brain by means of endothelial tight junction complexes. Development of the BBB is complex. It lies in the early communications of the embryonic endothelium with neural cells. BBB matures during fetal life and is well formed by birth.6,7 The BBB is structurally defined as specialised endothelial cells lining the intra luminal side of brain capillaries. It is a highly regulated interface that separates peripheral circulation and the central nervous system. It is estimated that every neuron has a capillary, human brain total length equals 650 km and capillary surface area available for molecular transport is as high as 20 m<sup>2</sup> (4)

Structural components of BBB

Components of BBB are neurons, Astrocytes, Microglia, Pericytes and blood vessels with specialised endothelial cells. The intimate contact between the above components and the functional interactions and signalling between them form a dynamic functional unit, known as the neurovascular unit. Neurons need a constant supply of oxygen and nutrients within 8–20 μm of distance



from capillaries. The brain homeostasis is critical and necessary because neurons are sensitive to many compounds and to subtle changes in their concentrations.(1)



**Blood Brain Barrier**

Neurons are also part of the neurovascular unit as their terminals arrive to all cells forming the BBB.<sup>13</sup> Endothelial cells Brain microvascular endothelial cells (BMVEC) are situated at the interface between the blood and the brain. They perform essential biological functions including barrier, transport of micro/macronutrients, receptor mediated signalling, leucocyte tracking and osmoregulation.(1)

- **Astrocytes**

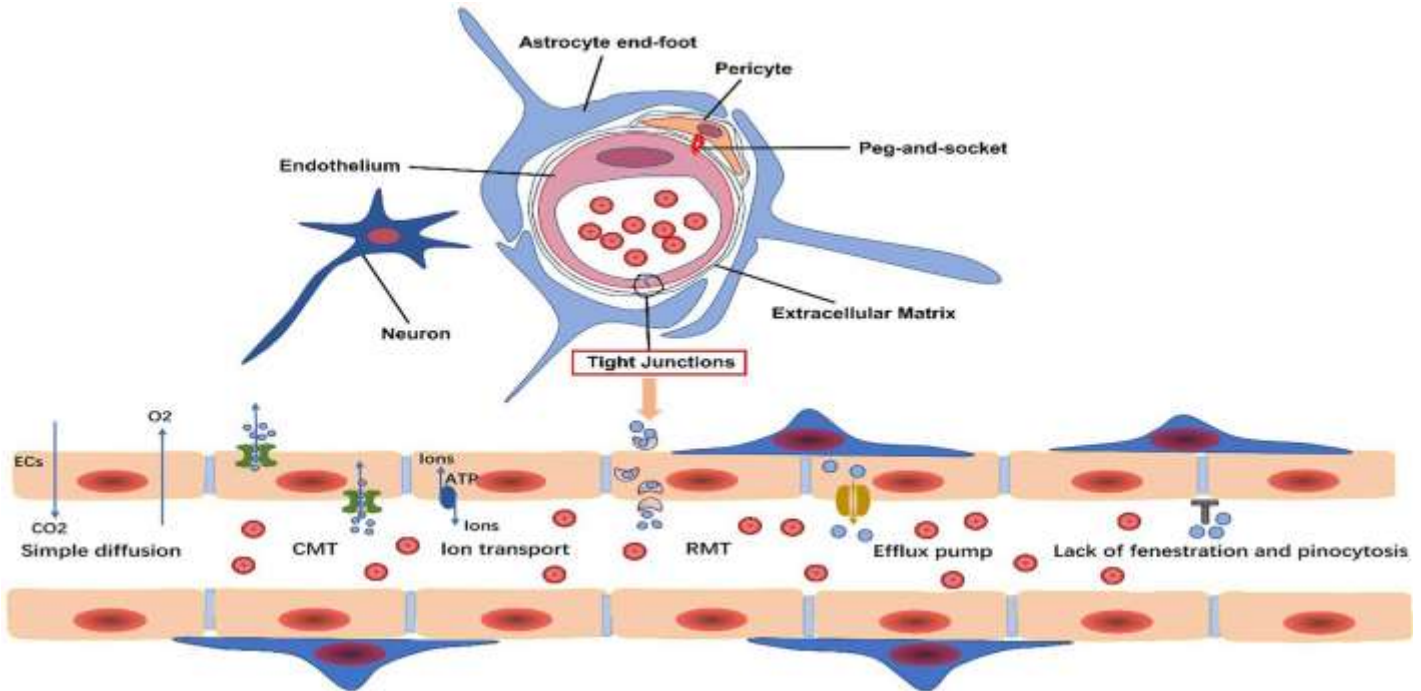
These are glia cells that envelop 99% of BBB endothelium. Astrocytes are essential for proper neuronal function and astrocyte-BMVEC interaction in the neurovascular unit. They are seen as the nerve glue or cement part of the structure. Astrocytes also play a role in sonic hedgehog signalling in the brain which suppresses expression of inflammatory mediators in the brain endothelial cells.(1)

- **Pericytes**

These are flat, undifferentiated, contractile connective tissue cells that develop around capillary walls. Association of pericytes to blood vessels has been suggested to regulate endothelial cell proliferation, survival, migration, differentiation, and vascular branching.(1)

### **TRANSPORT MECHANISMS INVOLVED IN BBB**

Essential substances cross the BBB via paracellular or transcellular pathways. This transport is strictly limited through both physical (tight junctions) and metabolic barriers (enzymes, diverse transport systems). Nutrients, ions and other molecules cross the BBB by paracellular diffusion through the junctional complex or by the transcellular pathway across the cells. Other factors that determine how easily the substance will passively diffuse through BBB include size less than 180 Da, fewer than 10 hydrogen bonds and lipid-soluble molecules. There are specific transporters that bring in essential nutrients. Essential nutrients, like glucose, are carried across the BBB by *slc2a1* also known as GLUT1. Other transporters include *slc16a1* for lactate and pyruvate, *slc7a1* for cationic amino acids, and *slc7a5* for neutral amino acids and L-DOPA.(2)



## ULTRA SOUND

Ultrasound is an oscillating sound pressure wave with frequency greater than upper limit of human hearing range. thus not separated from normal sound based on differences in physical properties, only the fact human cannot hear it.although this limit varies from person its it is approx 20kilohertz in healthy,young adults. (7)

## PHYSICAL PROPERTIES

Sound is a wave of energy that, unlike x-rays, must be transmitted through a medium. Sound waves can be described by their frequency, wavelength, and velocity. The frequency is the number of cycles or waves that are completed every second, and the wavelength is the distance needed to complete one wave cycle.

The frequency of the sound waves used in ultrasonography is well above the limit of the human ear (20,000 kHz) — usually in the range of 2 to 12 MHz (2 to 12 million Hz).

An inverse relationship exists between the frequency and the wavelength of a sound wave: the higher the frequency, the shorter the wavelength. This relationship affects the choice of frequency used in each patient undergoing ultrasonography. Higher-frequency ultrasound waves create higher-resolution images, but their shorter wavelength makes them unable to penetrate deeper tissues. Lower-frequency waves have better penetrating power, but because of their longer wavelengths, their resolution is lower. Weighing the need for higher resolution versus more penetrating power is always a consideration when selecting a transducer frequency. The velocity of an ultrasound wave is independent of the frequency. However, it changes depending on the medium through which the wave is traveling. For example, the velocity of sound is 331 m/sec in air and 4,080 m/sec in bone.<sup>2</sup> Within the soft tissues of the body, it is considered to be steady at about 1,540 m/sec.<sup>3</sup> This medium-dependent variation affects the ultrasound image produced (discussed below). (6)

The following equation demonstrates the relationship between frequency, wavelength, and velocity:

$$\text{Velocity (m/sec)} = \text{Frequency (cycles/sec)} \times \text{Wavelength (m)}$$



### WHY ULTRASOUND IS USED ?

- Ultrasound(US) is the most widely used imaging diagnostic tool in the world-wide.it is popular due the availability, speed, low cost and patient friendliness and no radiation. Applied in the urology,cardiology and obstetries. Ultrasound is a noninvasive diagnostic tool used to complement other imaging modalities.
- The degree to which the ultrasound beam penetrates the patient and the image resolution obtained depend on the frequency of the transducer used.
- Artifacts can be beneficial or detrimental to image interpretation.(8)

#### The Ultrasound Machine (8)

A basic ultrasound machine has a following parts:

1. Transducer probe: probe that sends and receives the sound waves
2. Central processing unit: computer that does all of the calculation and contains the electrical power supplies for itself and the transducer probe
3. Transducer pulse controls: changes the amplitude,frequency and duration of the pulse emitted from the transducer probe
4. Display : display the image from the ultrasound data processed by the CPU
5. Keyboard :inputs data and takes measurement from the display
6. Disk storage device: store the acquired images
7. Printer: prints the image from the displayed data
8. Transducer probe: probe that sends and receives the sound waves
9. Central processing unit: computer that does all of the calculation and contains the electrical power supplies for itself and the transducer probe
10. Transducer pulse controls: changes the amplitude,frequency and duration of the pulse emitted from the transducer probe
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13. Disk storage device: store the acquired image
14. Printer: prints the image from the displayed data

### FACTOR AFFECTING VESSEL PERMEABILIZATION

- Ultrasound parameter
  - Ultrasound frequency
  - Sonication time
  - Brust length
  - Transducer type
  - Pressure amplitude
  - Pulse repetition frequency
- Microbubbles
  - Concentration
  - Size
  - Nature (hydrophilic or lipophilic)
- Routes of administration
  - Intravenous bolus injection
  - Intravenous infusion

### FUTURE OF THE ULTRASOUND MEDIATED DRUG DELIVERY (10)

- its improved clarity for use in cancer diagnosis
- increased therapeutics use to correct blood clots and kidney stones
- portability and veterinary uses
- joint and muscle treatment through cavitation.
- In the treatment of the brain disorder like parkinsons, alzemer and other complicated brain disorder.
- Pancreas treatment



## CONCLUSION

The BBB remains to be one of the most insurmountable barriers in the drug delivery field. So that the therapeutics molecules cannot easily permeate this barrier. There are multiple physical principles, such as push-pull-mechanisms, microstreaming, microjets and shock waves, may contribute to US- and MB-mediated BBB opening, and non-invasive (MR) imaging may help to tailor efficient and safe sono-permeabilization. Ultra sound mediated drug delivery to brain may also become relevant for the treatment of neurodegenerative disorders, such as Parkinson's, Alzheimer's and Huntington's disease. To more efficiently and more rapidly move the field forward, concerted actions between several different basic and applied scientific disciplines are necessary, bridging biology, medicine, chemistry, physics and engineering, and involving input from both academia and industry, as well as from funding agencies, governmental bodies and health policy makers.

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