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Simulation on Drug Molecules Permeability of the Blood-Brain-Barrier

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Abstract

Blood-brain-barrier (BBB) mainly of tightly interconnected endothelial cells, which have specific function that set the brain apart from other cells in the body. It also can prevent the outer harmful substances from penetrating into the brain. So, most drug molecules can not reach the inner brain. In this paper, we establish a mathematical model to simulate the drug permeability of the blood-brain-barriervia considering the drug molecule size and the blood-brain-barrier permeability. The numerical results are computed via numerical parameters and the variation of drug concentration with respect to time is plotted via using MATLAB. The relationship between the concentration of the infiltrated drug varies over time in the brain is analyzed via considering the different permeability and the contact area, which shows that the internal drug concentration in BBB is proportional to the permeability and the contact area. The result is discussed via considering the molecule size and the blood-brain-barrier permeability.

Keywords

Blood-Brain-Barrier, Drug Delivery, Biofilm Permeability, Numerical Simulation, Mathematical Model

1. Introduction

Blood-brain-barrier(BBB) mainly consist of Human Brain Microvascular Endothelial Cells (HBMECs) and their tight junctions, adherent junctions, basal cells, pericytes, astrocytes and small cell margins. The BBB system contains a highly efficient enzyme system and a rich mitochondrial system, which is a dynamic interface with a selective barrier to keep balance of the brain's environment. BBB is the main barrier for drugs penetrating into the brain. BBB is very important in maintaining the specific microenvironment. The structure of BBB just likes a layer of endothelial cells surrounding the cerebral microvasculature (Figure 1), form the Figure 1, another function of BBB is to prevent injuries from external substance for its membrane connection. The BBB is a major obstacle to drug delivery for diseases of the central nervous system (CNS). Some invasive and non-invasive technologies are available to address the problem of drug delivery through BBB recently [1].

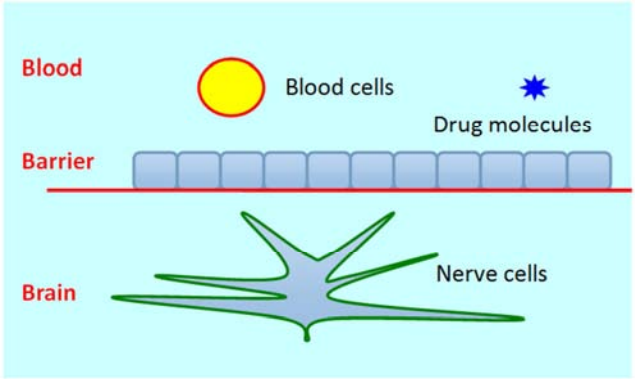

Figure 1. *The schematic diagram of blood-brain-barrier.*

Many models, both theoretical and experiment are conduct by scholars to explore the permeability of BBB. I-Chieh Chen et al [2], studied the toxicity and permeability of blood-brain-barrier in vitro model. The result shows that both AgNIs and Ag ions can cause discontinuous tight junction of some proteins of BBB such as claudin-5 and zonula occludens-1. The result also show

that the Ag ions may induced inflammatory cytokines to release, which has less cell-to-cell permeability than AgNIs. Andrew T. Placzek, et al [3], attends to think that the sobetirome is adrug can cross the BBB, and the author endeavorto increase the sobetirome permeability of BBB by using a prodrug strategy. The result shows that prodrug strategy applied to sobetirome could deliver increased concentrations of the active drug to the central nervous system (CNS). Seyed Nasrollah Tabatabaei, et al. [4], studied attend to think that the thermal energy generated by magnetic heating of commercially available magnetic nanoparticles may transiently increase the permeability of BBB. Many substances such as prolactin [5], ultrasound [6], herbal products of *Ginkgo biloba* [7], zinc [8], poteichoic acid and lipopolysaccharide [9], peptides [10], and some diseases (such as dementia, diabetes [11], Alzheimer's disease [12], systemic inflammation [13], partial hepatectomy [14]) are all regarded as the factor that could affect the permeability of BBB. The BBB not only plays an important role in protecting the brain from injury and diseases, but also restrains the delivery of potential therapeutic drugs for the treatment of brain illnesses. We have studied the mechanism and implementation of pulse electromagnetic fields affects the permeability of blood-brain-barrier via exploring the characteristics of fluorescence spectral of experimental rat [15]. The permeability of BBB is verified by the Evans Blue (EB) dye. Drug molecules are more likely to get through the blood-brain barrier of exposure rats. The result shows that the pulse electromagnetic field may induce the loose of the BBB. At the same time, other methods such as molecular dynamics (MD) simulation are used in this area [16]. Many pharmaceutical components, especially nano-particles are developed via computational design. So, mathematical model and its simulation on the efficacy of the pharmaceutical can be very helpful for predicting release profiles and evaluating process of drug delivery systems [17-20]. Now, computer simulation study on numerical models of drug release systems as a standard tool, it is commonly used in analyzing the release characteristics parameters of the drug system [21-23]. Among them, the most famous model-Weibull function is commonly used to fit drug release data [24-25], which was derived by assuming diffusion in devices with slab geometry and states that the amount of drug released is proportional to the square root of time. Release patterns in one and two dimensional systems can be obtained via Monte Carlo simulations, then, the method could be adjusted to the semi-empirical Weibull distribution function. At last, the size and porosity dependence analysis can be made on the two semi-empirical parameters of the Weibull function [25].

Despite many advanced technologies are used in neurology, drug delivery to inner brain still has a great challenge. Based on the previous work, in this paper, we establish a blood-brain barrier model to simulate its permeability by theoretical view.

2. Models and Methods

There are many factors that affect the drug molecules permeability of BBB. In order to study the permeability of BBB to drug molecules, the main affecting factors, such as the drug concentration, the size of drug molecules, the permeability of BBB itself, the permeability time, the contact area of the blood and BBB, etc are all considered to established a theoretical model as the following expression:

$$\frac{dy}{dt} = f\left(y, d, \alpha, S, t, ...\right) \tag{1}$$

Here, y is the drug concentration, d is the size of the drug molecule, $\alpha$is BBB permeability efficiency, S is the contact area of blood and BBB, t is time. In order to be able to clearly calculate the permeability of the drug molecule through BBB, it is now assumed that y, α, S, t is proportional to the drug transmittance, and d is inversely proportional to the transmittance of the drug molecule. Then we get the formula:

$$\frac{dy}{dt} = -y\frac{\alpha t S}{d} \tag{2}$$

Where the negative sign indicates that the concentration of the external drug in the brain decreases with time, and the drug concentration outside the brain can be obtained by solving the above equation, that is:

$$y = y_0 \exp\left(-\frac{\alpha S t^2}{d}\right) \tag{3}$$

Concentration of drugs within the brain can be written as y_0-y without considering the drug metabolism and the case of equal volume of the brain and outside. Then we use the MATLAB program to perform the equation and the numerical results are in the following.

3. Results and Discussion

For the formula (3), it is easily to give an intuitive result by assuming that the contact area of the membrane is 10^{-5} and the initial concentration of the external drug is 100. Figure 2 shows that the concentration of drugs penetrating into the brain changes over time in the case of different permeability efficiency (α=0.2-1) of BBB. Brain microvascular endothelial cells constitute the first barrier of the BBB system; it is mainly composed of flat brain microvascular endothelial cells and their junctions. There is only a layer of basement membrane between brain microvascular endothelial cells and astrocytes or pericytes. Close link can protect brain micro-environment stability, to prevent harmful substances into the central nervous system. In eq.(3), Close link is inversely proportional to the value α, just shown in Figure 2. From this perspective, Wei Gao, et al [16] put forward a novel strategy of rapid transport across the blood-brain barrier (BBB) via molecular dynamics (MD) simulation. The result of Wei Gao shows that the released drugs crossed the BBB via phosphatidylethanolamine-triggered release could perform their functions in the central nervous system. It is very

important for the development of CNS drug carriers.

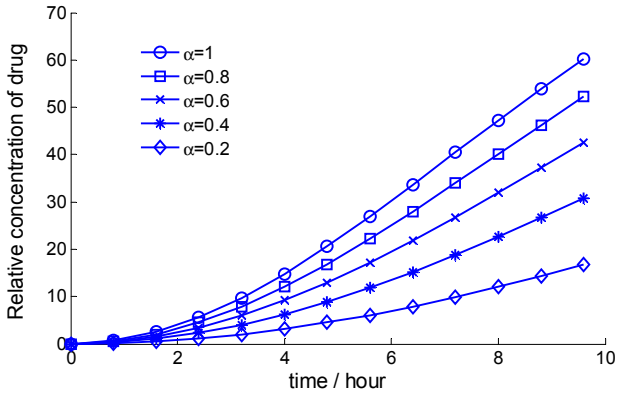

Figure 2. *Effects of different permeability on drug penetration results.*

Understanding of the properties of the BBB is essential in developing effective treatments for the brain and other CNS disorders. CNS drug screening of new drugs has been a bottleneck in the field of medicine. There are a variety of interference factors; it is a high cost study of exploring the permeability of BBB in vivo. Here is the case of taking into account the situation of local administration (volume of body fluid concentration equivalent both inside and outside the brain) and without considering the drug metabolism. In addition, in the same circumstances, we also considered the brain outside the initial drug concentration is 100, the permeability efficiency α=1, contact area of BBB inside and outside is between $(0.1\text{-}0.5)\times10^{-5}$, The relationship between the concentration of the infiltrated drug over time in the brain is shown in Figure 3, that is, the result of osmotic concentration is proportional to the contact area.

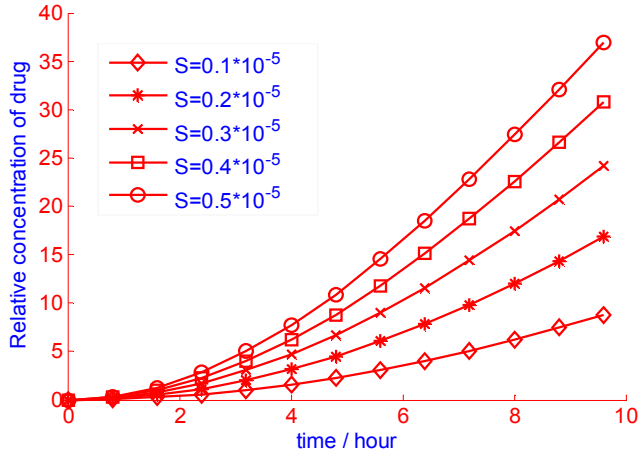

Figure 3. *Effects of different contact area on drug penetration.*

Recently, drug penetration through BBB gradually attracts different scientific disciplines attention for its very important functional structure. In particular, the study of drugs through the BBB in the treatment of neurological diseases has become extremely important. At the same time, most mathematical model for BBB is based on the probability model. For it is clear that a tight junction of the BBB represents a complex junctional structure, and many models of the BBB consists of a few essential transmembrane proteins, forming a delicate multifunctional cytoarchitecture [26-28]. Age-related neurological diseases, such as Alzheimer's disease, stroke, brain tumors continue to increase with the aging of the population. Therefore, exploring new ways to treat these diseases via effective drugs is very important, and a profound understanding of the cytological structure of the blood-brain barrier is very helpful not only for understanding the molecular mechanism of the function of the blood-brain barrier, but also for the seeking new strategies to treat nervous system diseases.

4. Conclusion

The BBB not only can protect the brain from the intrusion of harmful substances, but also presents as a major obstacle for the treatment of many CNS disorders and diseases. For all types of BBB drug transport mechanism of the model is not yet perfect, in this paper, the theoretical calculation model of BBB penetration is established. Combining with classical model, the composition and characteristics of the model are analyzed, which shows that when the permeability efficiency and the contact area are concerned respectively, the relationship between the concentrations of the infiltrated drug over time in the brain is calculated and result of osmotic concentration is proportional to them. The results can provide reference for drug screening and study the BBB penetration mechanism.

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