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NANOPARTICLE-INFUSED DRUG DELIVERY SYSTEM FOR SUBDUING BLOOD-BARRIER IN ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative condition that is defined by the deposition of amyloid-beta plaques and neuroinflammation in the brain. The disease progresses slowly over time. The existence of the blood-brain barrier (BBB), which hinders the transport of medicines to the brain, is one of the key obstacles that must be overcome in order to treat Alzheimer's disease (AD). This work presents a unique nanoparticle-infused medicine delivery method with the goal of successfully combating AD pathology and overcoming the BBB. The suggested method combines the benefits of nanoparticles with targeted medication administration in a single delivery device. Nanoparticles that are biocompatible and can be loaded with therapeutic medicines have been produced by our team. These nanoparticles are able to reduce amyloid-beta plaques and alleviate neuroinflammation. These nanoparticles have been designed to go over the BBB and deliver their payload directly in the brain areas that are being damaged.

Keywords: *Drug Delivery, Blood-Brain Barrier, Alzheimer's Disease*

INTRODUCTION

Over 50 million individuals throughout the world are living with Alzheimer's disease (AD), which results in a health burden that costs more than 1% of global GDP. Alzheimer's disease is associated with a buildup of a protein called amyloid-beta (Abeta) in the brain, which can then aggregate into fibrils and plaques in the extracellular space of the brain. Additionally, tau fibrils and aggregates can be found forming in the brain, which can lead to intracellular neurofibrillary tangles. It is considered that Alzheimer's disease is a state of chronic neuro-inflammation. This neuro-inflammation may induce the gradual development of amyloid beta or tau fibrils and aggregates, which ultimately results in dystrophic neurites. New therapies for Alzheimer's disease focus on reducing the amount of aggregated Abeta and/or tau, reducing neuroinflammation, and repairing dystrophic neurites. Since many years ago, researchers have been able to identify the underlying pathology of Alzheimer's disease. In spite of the huge efforts being made all over the world to discover new medications for Alzheimer's disease (AD), the Food and Drug Administration has not given its approval to a new therapy for AD since the year 2003.

The idea that the blood-brain barrier (BBB) is the single most important factor in explaining why there aren't any new therapies for Alzheimer's disease is the central thesis of this review. To begin, greater than 98% of all small-molecule medications and greater than or equal to 100% of all biologic therapies are unable to pass the blood-brain barrier. Second, the pharmaceutical industry has been sluggish to create BBB drug delivery technology that is capable of being applied to clinical trials involving humans. An examination of the relevant

published material by Pubmed reveals a shocking lack of advancement in blood-brain barrier medication delivery technology. If you search 'Alzheimer's disease medication development' in Pubmed as of October 2020, you will find 9837 citations. When you search for 'Alzheimer's disease medication development and blood–brain barrier drug transport' in Pubmed, you get 191 citations, which is 1.9% of all results. Over ninety-nine percent of all Alzheimer's disease medication research initiatives are carried out in the absence of BBB drug delivery technology, despite the fact that more than half of these citations refer to nanoparticles, which have shown to be challenging to transfer to human neurotherapeutics.

The abundance of "BBB avoidance strategies" is one of the factors that contributes to the pharmaceutical industry's lack of progress in the area of the development of BBB drug delivery technology. These methods of drug transport to the brain are discussed more below. They drive neuropsychiatric drug developers to conduct clinical tests on medications that do not enter the brain, which eventually results in the clinical trial being unsuccessful. Another issue is that measuring the transport of drugs over the BBB is not a standard practice, and the techniques that are applied are prone to producing artifacts, as will be explained in more detail below. The process of how tiny molecules can pass through biological membranes like the blood-brain barrier (BBB) is analyzed first, before any clinical trials on small molecule therapies for Alzheimer's disease are looked at. Large molecules, such as those found in biologic medications, are able to pass through the blood-brain barrier (BBB) with only limited success after being given in a systemic dose. Despite this, several other biologics have entered clinical trials for AD, and we will explore these. Finally, the re-engineering of biologics as BBB-penetrating IgG fusion proteins is discussed in the context of a combined therapy plan for Alzheimer's disease. This treatment plan targets various aspects of the illness, such as neuro-inflammation, the removal of aggregates of Abeta or Tau, and the repair of dystrophic neurites.

Blood–Brain Barrier Avoidance Strategies

There are a few different BBB avoidance tactics that a CNS medication developer might use in order to enter a clinical trial without a BBB drug delivery system. These options are discussed further below. These BBB avoidance tactics have not resulted in the FDA approving any novel medications for Alzheimer's disease, as will be explained below.

Drug Distribution in CSF Used as a Measure of BBB Drug Transport

If a medicine is discovered to diffuse into cerebrospinal fluid (also known as CSF), then it is considered to have crossed the blood-brain barrier. Drugs can get into the CSF, but they can't get over the blood-brain barrier. This is due to the presence of two different barriers in the brain, as described in The brain capillary endothelial wall and the choroid plexus are the two structures that make up the blood–CSF barrier and the blood–brain barrier, respectively. Within the brain parenchyma, the blood–brain barrier (BBB) is located at the brain capillary and separates blood from brain interstitial fluid (ISF), whereas the blood–cerebrospinal fluid (CSF) barrier is located at the choroid plexus and separates blood from CSF. Drug delivery through the choroid plexus epithelial barrier is necessary for drug transport into the cerebrospinal fluid (CSF), whereas drug delivery across the brain capillary endothelial barrier, which forms the blood–brain barrier (BBB), is necessary for drug transport into the intraspinal fluid (ISF) of the brain. Because it is considered that CSF is in equilibrium with brain ISF behind the BBB, the distribution of drug into CSF is employed as a proxy for measuring drug penetration into the ISF of brain parenchyma. This is because the BBB separates the CSF

from the brain ISF. This is not the case, however, because the BBB and the choroid plexus are two separate barrier membranes that are both physically and functionally distinct from one another.

When compared to the BBB, the choroid plexus has a leakiness factor that is greater than one hundred. The electrical resistance measured across the choroid plexus, which was 26 ohm, is significantly lower than the electrical resistance measured across the blood–brain barrier, which was 8000 ohmcm2. All medications in plasma passively diffuse to the cerebrospinal fluid (CSF) in a way that is inversely linked to their molecular weight (MW), which is caused by the relative leakiness of the choroid plexus. For instance, plasma proteins like albumin and IgG are able to readily flow into the cerebrospinal fluid, and the ratio of IgG levels in the plasma and CSF is 0.22%, as illustrated in.

This discovery is used to support the concept that the ratio of IgG in brain, relative to plasma, is also 0.2%; as a result, there is a tiny but considerable transit of therapeutic antibodies across the BBB. The ratio of IgG in CSF, compared to plasma, was found to be 0.2%, and this finding is used to support the hypothesis that the ratio of IgG in brain, relative to plasma, was also 0.2%. However, as a measure of antibody transport across the BBB, one should look at the distribution of a therapeutic antibody in brain tissue rather than in CSF. When brain tissue is examined, the ratio of a therapeutic antibody's concentration in the brain to its level in plasma is less than 0.01%, as demonstrated in By creating the false impression that the therapeutic antibody is able to pass across the BBB and validating the admission of the therapeutic antibody into AD clinical trials, the distribution of therapeutic antibodies into cerebrospinal fluid (CSF) can be used as a surrogate for the transport of therapeutic antibodies across the BBB. Despite the fact that more than 20 therapeutic antibodies are now participating in AD clinical trials, no therapeutic antibodies have yet to be licensed for the treatment of Alzheimer's disease (AD), as will be discussed below.

OBJEACTIVES

1. The Study Nanoparticle-Infused Drug Delivery System.

2. The Study Blood-Brain Barrier, Alzheimer's Disease.

RESEARCH METHODOLOGY

The developers of CNS drugs need to be aware of the prospective drug's ability to breach the blood-brain barrier. The measurement of BBB drug transport is complicated by the absence of a universally accepted technique, as well as the fact that many of the most popular methodologies suffer from certain kinds of technological constraints.

In Vitro Models of BBB Transport

An in vitro model of the blood-brain barrier (BBB) may be created by isolating the brain capillary endothelial cells and growing them in cell culture. However, this model that is over four decades old has been unable to recreate the transport features of the BBB in vivo. This is because there has been a significant reduction in the BBB tissue-specific gene expression in culture. Even the most advanced in vitro BBB models, which were produced relatively recently, are still one hundred times more permeable than the BBB in vivo. As a result, manufacturers of drugs for the central nervous system (CNS) cannot depend only on drug transport through in vitro BBB models as a measure of drug entrance into the brain in vivo.

Small Molecule Drugs for Alzheimer's Disease

It is commonly accepted that small molecule medications may cross the BBB without the need for a delivery mechanism, which results in a development process that is far more expedient than that for biologic therapies. However, only 5% of all medications in the Comprehensive Medicinal Chemistry database are active in the central nervous system. These pharmaceuticals are only active for the treatment of affective disorders and insomnia. This means that there are 95% of all small molecule drugs that are active in the brain that do not treat affective disorders. Another study found that 12% of all medicines were active in the central nervous system, but this percentage plummeted to 1% when affective diseases were taken out of the equation.

The chemical characteristics of small molecules that permit passage over the BBB are the reason why there are so few small molecule medications that are active in the central nervous system (CNS) outside of affective disorders. To begin, there is a significant reduction in BBB transport if the MW of the medication is more than 400 Da. Second, the medicine is considered to be too polar to pass through the BBB if the polar functional groups on the drug produce bonds other than hydrogen bonds. If the polar surface area (PSA) of the medication is more than 80, which is equivalent to having a molecular weight of 400 Da, then the transport across the BBB is very low. When the PSA is increased from which corresponds to a MW of 300 Da to a PSA of 105, which corresponds to a MW of 450 Da, there is an exponential drop in the amount of BBB transfer that occurs. Affective disorders, pain, sleeplessness, and epilepsy are the only types of brain illnesses that have been shown to respond to tiny molecules with a MW and a hydrogen bond number of. This is a rather small number of brain disorders. As will be shown in the next section, the only tiny molecules that have been given the go-ahead to treat Alzheimer's disease are called acetylcholinesterase inhibitors (ACEI). These medications have a molecular weight (MW) ranging from 179 Da to 380 Da and create hydrogen bonds with the solvent water.

Because medications found via receptor-based high throughput screening (HTS) inevitably have a certain molecular weight (MW), the MW threshold for BBB transfer of small molecules is the limiting factor in the development of novel small molecule therapies for neurodegenerative disease. The technique of transporting tiny molecules through phospholipid membranes, which ultimately results in the formation of the MW threshold, is depicted in According to the traditional Overton model of solute free diffusion through membranes, the permeability coefficient, denoted by "P," is a function of the lipid partition coefficient, denoted by "K," the drug diffusion coefficient, denoted by "D," and the thickness of the membrane, denoted by "d," as detailed in A. In this model, "K" refers to the K in a model solvent such as 1-octanol. The Overton model is not dependent on MW in any way.

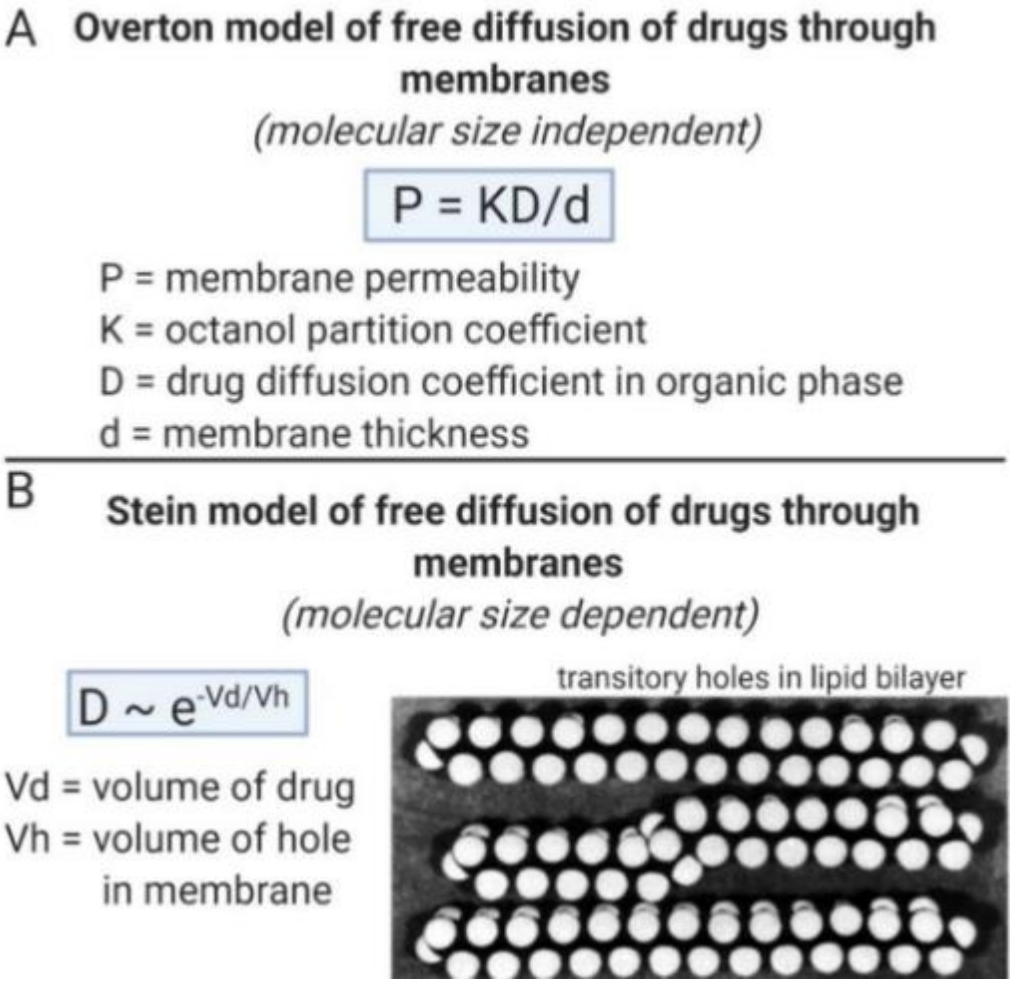

Figure 1. The Overton model of solute free diffusion through biological membranes defines the membrane permeability as a property of lipid solubility, diffusion coefficient, and membrane thickness, and is independent of the molecular weight (MW) of the solute (B) In the Stein model of solute diffusion through biological membranes, the drug diffusion coefficient is dependent on MW, in that MW is generally proportional to the molecular volume (Vd) of the drug. The drug diffusion coefficient decreases exponentially as the Vd increases relative to the volume of membrane holes (Vh) The membrane holes through which the solute penetrates the membrane are formed by the transitory kinking of fatty acyl side chains of membrane phospholipids; the membrane model is adapted from Trauble with permission. Image created with Biorender.com.

Re-Engineering Biologics as BBB-Penetrating IgG Fusion Proteins for Alzheimer's Disease

L-DOPA is a neuroactive medicine for the treatment of Parkinson's disease (PD) due to the fact that this neutral amino acid drug is able to cross the blood-brain barrier (BBB) through the large neutral amino acid carrier-mediated transport (CMT) system on the BBB, which is the type large neutral amino acid transporter (LAT1) system. These endogenous CMT systems are possible portals of entry into the brain for small molecule CNS medicines that have been changed to permit transport over the BBB on the CMT systems. Many more CMT systems are expressed on the BBB for different classes of minerals, vitamins, or hormones. In a similar fashion, receptor-mediated transport (RMT) systems are produced inside the BBB in order to mediate the transport of endogenous peptides. Some examples of these include insulin, transferrin (Tf), leptin, and the

insulin-like growth factors (IGFs). The peptidomimetic monoclonal antibodies (MAbs) that bind exofacial epitopes on the BBB receptor are also transported by the RMT systems of the BBB. Because of this interaction, the antibody is able to "piggyback" across the BBB on the endogenous RMT system. Since more than 25 years ago, researchers have been aware of the receptor-mediated transport (RMT) of certain antibodies across the BBB. This was demonstrated for a TfRMAb in a rat and an HIRMAb in a Rhesus monkey. These BBB-specific antibodies have the potential to serve as a molecular Trojan horse in order to deliver biologic drugs, which are unable to pass the BBB on their own.

Earlier research utilized avidin-biotin technology to couple the medication to either the TfRMAb or the HIRMAb in order to facilitate the transport of biologics across the BBB. A monobiotinylated peptide, such as vasoactive intestinal peptide (VIP), or the Abeta peptide was attached to a chemical compound of streptavidin and the TfRMAb or HIRMAb. This allowed the peptide to be detected with either antibody. After that, genetic engineering was employed to create IgG fusion proteins, which involved fusing the biologic with either the TfRMAb or the HIRMAb. All kinds of biologics, such as enzymes, decoy receptors, neurotrophins, and therapeutic antibodies, were fused to a TfRMAb or an HIRMAb Trojan horse, and model IgG fusion proteins are presented in for a decoy receptor, a therapeutic antibody, and a neurotrophin. [Citation needed]

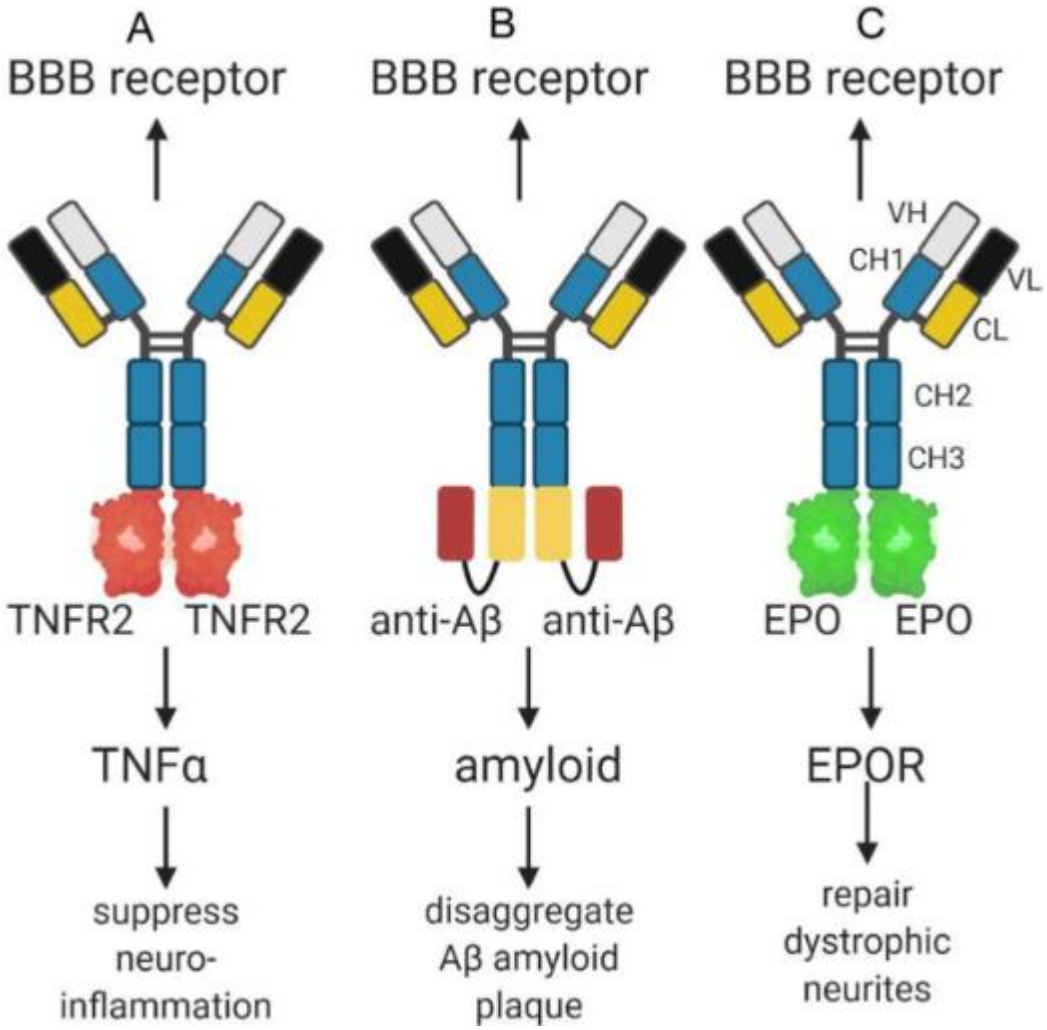

Figure 2. IgG-TNFR2 fusion protein formed by fusion of TNFR2 extracellular domain (ECD) to carboxyl terminus of the heavy chain of a monoclonal antibody (MAb) against the BBB insulin receptor (IR) or transferrin receptor (TfR). The fusion protein both binds the receptor on the BBB, to enable entry into brain, and sequesters TNFα in brain to suppress neuro-inflammation. (B) Bispecific antibody formed by fusion of a single chain Fv anti-Abeta antibody to the carboxyl terminus of the heavy chain of a MAb against the BBB IR or TfR. The fusion protein both binds the receptor on the BBB to cause penetration of the brain, and disaggregates amyloid plaque in brain behind the BBB. (C) IgG-erythropoietin (EPO) fusion protein formed by fusion of EPO to the carboxyl terminus of the heavy chain of a MAb against the BBB IR or TfR. The fusion protein both binds a receptor on the BBB, to trigger entry into brain, and binds the EPO receptor (EPOR) in brain to induce neuroprotection. Image created with Biorender.com.

DATA ANALYSIS

Convection-enhanced drug delivery (CED)

The CED technique is a form of local or regional micro infusion that is administered specifically to the brain's tissue. The distribution of therapeutic drugs into the interstitial space is the consequence of a continuous infusion pressure gradient that occurs over the course of hours to days. The CED method is utilized most frequently for large molecular weight agents, including as viruses, oligonucleotides, nanoparticles, liposomes, and targeted immunotoxins. These compounds exhibit limited leakage over the BBB and/or have considerable systemic toxicity. Infusion parameters (rate, volume, duration, and cannula size), infusate characteristics (molecular weight, surface properties, and tissue affinity), and tissue properties (tissue density, extracellular space, vascularity, and interstitial fluid pressure) are the parameters that affect the volume of distribution of CED. Studies conducted on animals have shown that the volume of distribution that can be obtained by CED may be observed by magnetic resonance in real time by incorporating contrast ants inside the infusate. This was accomplished.

The most important use of CED in clinical practice will be for the targeted treatment of glioblastoma. Recent trials have investigated radioimmunotherapy with mAbs targeting tenascin or tumor necrosis factor, as well as interleukin 13/pseudomonas exotoxin alone or in combination with radiation/temozolomide. It appears that none of the two industry-sponsored phase III studies with CED immunotoxins had a positive outcome, despite the fact that the early results were quite encouraging. Inhomogeneous distribution of the CED therapy, high interstitial fluid pressure, and fast agent efflux from the injection site are some of the mechanisms that contribute to failed CED treatment. In order to circumvent these challenges, it is necessary to acquire a longer residence period in order to improve the targeted toxin receptor binding and absorption by the malignant cells. The CED method primarily targets brain tumors; however, there is a possibility that it might also be used to treat localized neurodegenerative illnesses. For instance, CED was used to inject 6 glucocerebrosidase into the frontal lobe and brainstem of a patient suffering from neuronopathic Gauche illness. This was accomplished by targeting specific areas of the brain. In patients with Parkinson disease, the administration of adenovirus vectors or glial-derived neurotrophic factor has been evaluated.

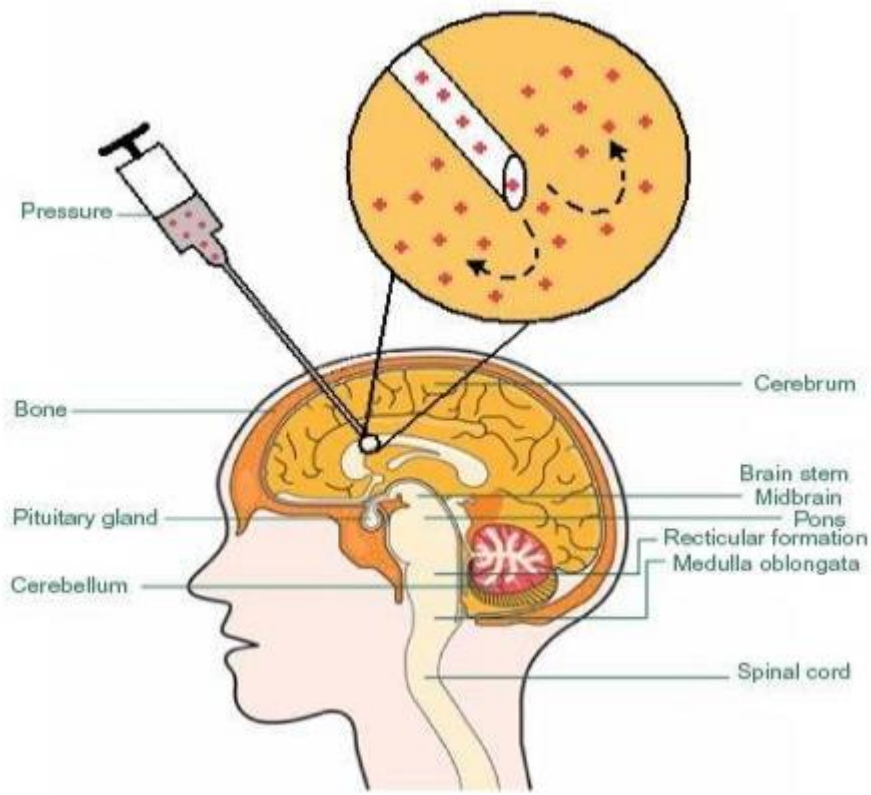

Figure 3: Illustration convection-enhanced drug delivery

Bradykinin receptor-mediated BBB opening

A transitory increase in blood vessel permeability can be induced by the endogenous peptide mediator of the inflammatory response known as bradykinin. This increase in blood vessel permeability can be very selective for the vasculature of tumors. RMP-7, also known as lobadimil, is a synthetic bradykinin analog that is selective for the B2 receptor. In mice, its activity is one hundred times more powerful than that of bradykinin. The use of pharmacological modulation of the BTB presents the opportunity for extremely selective opening and targeted drug delivery to the tumor, despite the fact that gains in delivery may only be minor and rely on the kind of tumor or animal being treated. Research conducted in hospitals over the past five years has shown that treating adults and children with gliomas simultaneously with RMP-7 and carboplatin is safe, regardless of whether or not radiation therapy is also administered. However, RMP-7 did not influence the pharmacokinetics or toxicity of carboplatin, and two trials have demonstrated that RMP-7 and carboplatin do not produce any objective responses in brain stem glioma or high-grade glioma. In order to improve carboplatin transport to the tumor, higher dosages of RMP-7 could be necessary; however, this might also result in greater toxicity in normal brain tissue.

Ultrasound (US)-mediated BBBD strategy

The United States is made up of pressure waves that have frequencies of at least 20 kilohertz. Ultrasonic waves, just like optical and audio waves, have the ability to be focussed, reflected, and refracted as they travel through a material. It was believed, for a number of decades, that the skull bone needed to be removed in order to undertake ultrasound treatments inside the brain. This was a significant barrier to the use of ultrasound for the treatment of BBBD since ultrasound has a poor penetration through the skull. However, both practical

and theoretical research has demonstrated that it is possible to obtain targeted, trans-skull focused ultrasound (FUS) exposure of brain tissue by the utilization of large surface area phased arrays. This has been demonstrated to be a realizable goal. Recent developments in image-guided (for example, magnetic resonance imaging [MRI]-guided) FUS clinical systems have made it feasible to administer treatments to the targeted locations in the brain via the unbroken skull. Both animal research and clinical trials have showed good outcomes thus far.

As seen in the figure, ultrasonic microbubbles paired with FUS have the potential to function as drug carriers that can accomplish targeted distribution. Microbubbles that have been preformed and have a confined size distribution have been employed in order to create a cavitation environment that is reproducible and has a regulated source of cavitation nuclei. The phenomenon known as cavitation may be described as the oscillation of bubbles in the presence of an acoustic field. Cavitation has the potential to induce severe stressors on cells, which can then result in a variety of "bioeffects." For instance, it may result in the physical shearing of the cell membrane in order to allow the direct entry of medicines into the cytoplasm. Additionally, it may increase the likelihood of a drug interaction by upregulating the pathways of various forms of stress response. The amount of acoustic energy required by the cavitation will be significantly cut down when ultrasonic microbubbles are present in the blood vessels. Because of this approach, the process is now more amenable to application via the intact skull. This is because the dangers of overheating the skull would be greatly decreased thanks to this technology. In addition, the use of these medications makes it possible to restrict the contact of the US with the endothelial cells, which in turn makes it possible to reduce the likelihood that other brain structures will be damaged.

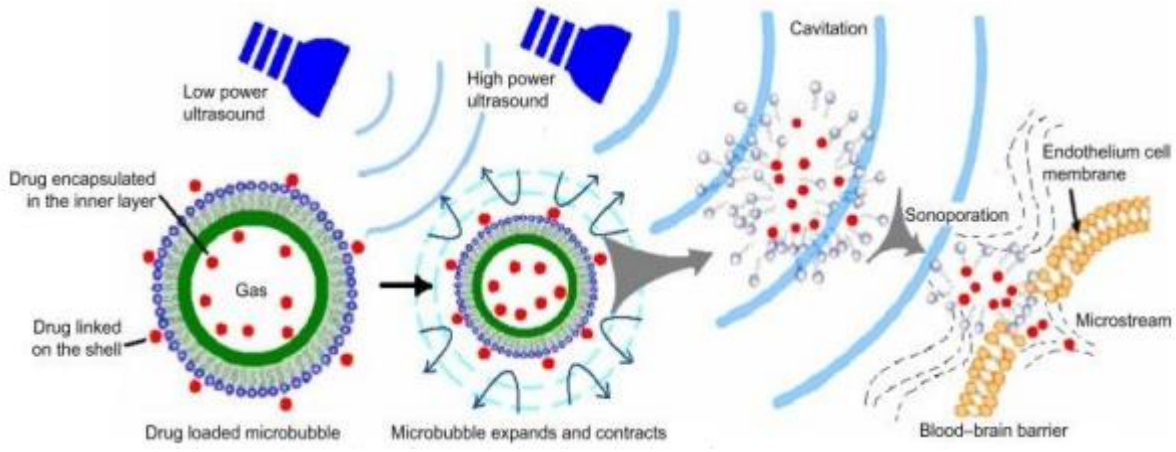

Figure 4: Illustration of Ultrasonic Microbubbles for Drug Targeted Delivery

CONCLUSION

The creation and optimization of the nanoparticle formulation is discussed here, with an emphasis placed on the formulation's stability, drug release kinetics, and biocompatibility. In addition, we investigate a variety of methods for directing these nanoparticles to AD-specific brain areas, which increases the therapeutic efficiency of the nanoparticles while reducing the number of unintended side effects. Experiments done in vitro and on living subjects are also a part of the research project, and their purpose is to verify that the nanoparticle-infused medication delivery system is successful. Our findings show considerable enhancements

in cognitive performance and decreases in AD-associated pathology in animal models, lending credence to the possibility that this technique may be used to treat AD.This study demonstrates a potentially useful nanoparticle-infused medication delivery technology that may be used to break down the blood-brain barrier in patients with Alzheimer's disease.

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