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Nano particle targeting brain system

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ABSTRACT

The drug delivery to the brain system is a most challenge to the scientist for developing the drug designed for CNS. The major problem is that all the drugs does not passes through BBB, only nanoparticles and highly lipid soluble drugs may pass through. The BBB is a most essential barrier between the circulating blood and the neural tissue. The criteria for drug delivery includes the following, a) the drug must be stable, b)the drug must have access to brain, c) the dose should be sustained and controlled, d) the effect of drug should be localized. The drug may administer either by systemic administration or by direct delivery of drugs into the brain. The polymers which plays an most important role in the advancement of drug delivery technology by providing controlled release of therapeutic effect, administered in the constant dose over a long period of time. The BBB maintains the brain homoeostasis as well as movement of ion and molecule. Failure in this process results in breakdown of brain cell structure. This may leads to a disease such as Parkinson disease and Alzheimer's disease.

Keywords: Nanoparticles, blood brain barrier (BBB), polymers, controlled drug release.

INTRODUCTION

Drug targeting is the ability of the drug to accumulate in the targetted tissue or organ, quantitatively and selectively and they are Independent to the site and route of administration. The drugs which have been targeted should have the greater affinity towards the specialized cells. The main action or the function is first to recognizes and binds the target and provide the therapeutic action in this target. It includes corresponding behavior of three components, such as targeting moiety, drug and carrier.

Drug delivery to the brain is the process of transport of active molecules across the blood brain barrier for the purpose of targeting brain diseases. Due to lack in the conventional delivery mechanism, aggressive research

has develop the new strategies to make a drug molecules to deliver more effectively to the CNS.

Some direct route of administration to brain is more invasive- transnasal route & other entry into CNS by devices and needles-intrathecal and intra cerebroventricular, various route of administration and conjugation of drugs, such as liposomes and nanoparticles are considerd [1,2].

ANATOMY, BRAIN, BLOOD BRAIN BARRIER

The blood-brain barrier is the most important barrierin the brain, presentbetween the cerebral capillary and the interstitial fluid. It is a high selective semipermeable membrane made up of thight junction of capillary endothelial cells and basement membrane with astrocyte and pericytes. The entry of various toxicsubstances and microbs into the cerebral blood flow and the brain parenchyma cells may prevent by this components[3]. The structure of BBB is given in fig 1.

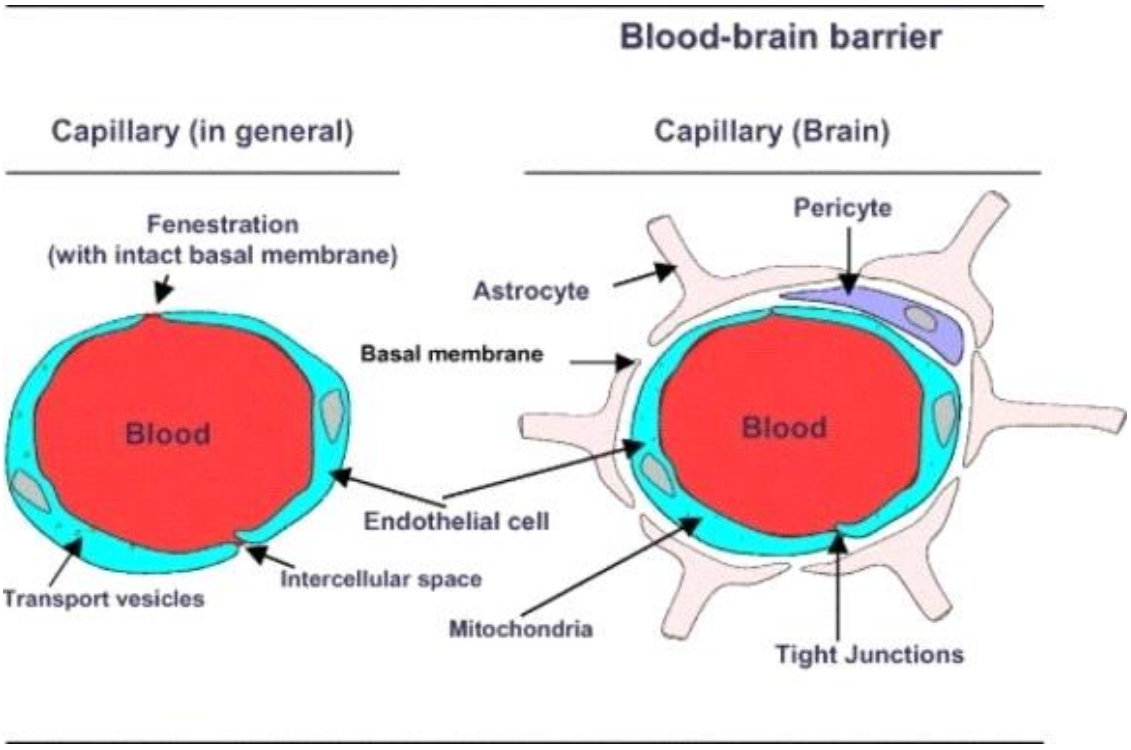

Fig 1: Structure of Blood Brain Barrier

Structurally the brain is highly unique, thus it requires the homeostatic environment to maintain the stable condition which was maintained by blood brain barrier system. Thus the CNS may function properly which may regulate by several mechanisms [2, 3].

EMBYOLOGY

The blood-brain barrier development begins with the angiogenesis, in which the preexisting vessels, conductedby the factor called vascular endothelial growth factor (VEGF). This give rise to new vessels by perfuses the formation of neuroectoderm. In early stage the new vessels formed by the neuroectoderm may started to exhibit many function of the BBB, including the expression of tight junctions and providing nutrient transporters, which will later plays a role in the selectivity of this physiologic barrier. These vessels consist of high levels of transcytotic vesicles and leukocyte adhesion molecules (LADs) [4].

This mature as an endothelial cells of the perinuclear vascular plexus, which may leads to a development of tight junction's endothelial cell between 11 to 13 days of gestation. These barrier leads to the formation of tight junctions, down regulation of leukocyte adhesion molecules, decreased transcytosis, and increased expression of efflux transporters in the cell membrane.

The sealing and inter-endothelial tight junctions were formed at the final stages of maturation [5,6].

FUNCTIONS

- The blood-brain barrier has a vital role in maintaining homeostatic environment within the central nervous system. It was regulated by the tight junction of endothelial cells in the BBB.
- These tight junctions of endothelial cells in BBB may only allow the passage of few substances, such as glucose, ions, oxygen, and other special molecules may pass through.
- The hydrophilic substances, and large molecules may not able to cross the BBB whereas the lipophilic substance may pass through, since brain is highly lipophilic in nature
- The entry of toxic substances and other foreign substances may prevent by the blood brain
- The bicarbonate ion and hydrogen ions is impermeable to BBB but the CO2 can pass through, and which converted into bicarbonate and hydrogen molecules within the brain [7].

PROBLEM FACED IN THE DRUG DELIVERY DUE TO BBB

The tight junction of the endothelial cell in the BBB may not allow the larger molecules, proteins and the lipophilic drug to pass through the barrier. However, the highly lipophilic drug may penetrate easily. By passive diffusion process the fat substance penetrate into the cell membrane and cross the barrier. The highly electric charge molecular may have low penetration in BBB. The major problem in the drugdelivery to the brain is the hydrophilic drugs, since it does not pass the barrier. Thus the drugs should be converted into nanoparticles in range and make them more lipophilic, then it will easily pass through the barrier.

NANO PARTICLE

Nanoparticles are the colloidalsolid matrix like particles made up of lipids or polymers. The polymers play a role in controlled drug release system. They are administered through intravenous route like the liposome. The most important advantages of liposome's is very less number of excipient is used for the preparation, and their size ranges from 10-1000nm. It is generally about 50-300nm in range, like liposome they are not able to cross the BBB, and thus not enters into the brain parenchyma. The BBB is the major confront towards the brain targeted drug delivery.BBB is highly permeable barrier that separate the extracellular fluid in CNS and the circulating blood from the brain [7,8].

The nanoparticle are of two types, namely,1) Nano spheres& 2) Nano capsules. The nanospheres are the spherical particles having nanometric dimension and acting as a drug carrier in which drug is enclosed inside the polymer matrix. The Nano capsules contains inner liquid core containing drug, and outer surface of nanoparticles are surrounded by the polymeric membrane [9,10,11].

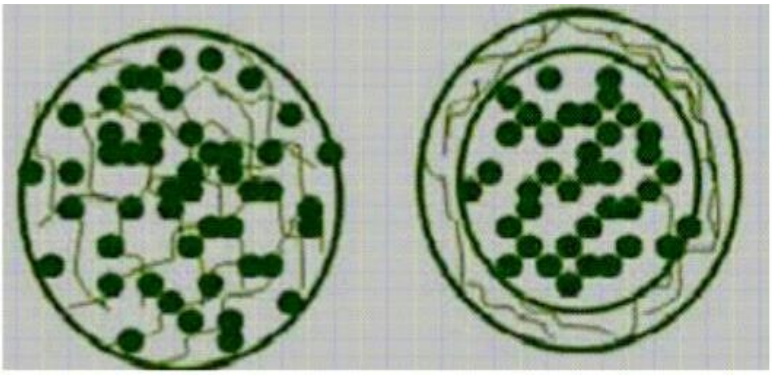

Fig 2: A)Nano sphere B) Nano capsules

The BBB have an efficient ability to restrict and separate the human brain from circulatory network and only allow the transportation of molecules that play a vital role in the functional activity of brain. The BBB does not cross by almost 100% of large molecules of drugs & 985 of small molecules of drugs. NDDS is the

most cutting edge innovations that can be used to convey sedate particles straightforwardly into the mind and ended up being extremely successful against a few CNS issue.

The neurological disorder is an important cause and it constitutes 12% of total death globally. The neurological disorders include Alzheimer disease, Parkinson disease, epilepsy, etc [12,13].

NANOPARTICLE CONJUGATED CARRIER

The nanoparticle should be coated with suitable polymer which provides the controlled release of the drug. The coated polymer is attached with the targeted ligand target. This targeted ligand binds with the carrier in the brain and then it passes into the targeted site [14,15,16].

POLYMERS USED FOR BRAIN TARGETING POLYMERS

The term polymer is derived from the ancient Greek word (POLY, meaning MANY) and (MER, means PARTS) and are refers to the molecules whose structure is composed of multiple repeated subunits units of monomers. They are prepared by polymerization process, by means of small molecules of monomers. The polymer has the properties of toughness, viscoelasticity and a tendency to form glasses and semi crystalline structure rather than crystals. The polymer have assumed an imperative part ahead of time of medication conveyance innovation by giving controlled arrival of remedial operators in the consistent measurement over extensive stretches, cyclic dose[17].

TYPES

They are of classified into three types namely natural, synthetic and semisynthetic.

NATURAL

These are biopolymers which produced by living organisms, they are polymeric biomolecules. They include protein and polysaccharides. Some of the protein polymer such as Gelatin, Albumin, etc... The polysaccharide polymers such as Chitosan, Alginate, Dextran, Hyaluronic acid, Carrageenan, chondroitin, heparin, etc..

SYNTHETIC

They are human made polymers, the common backbone of synthetic polymers is polymers, polystyrene and poly acrylates. The some of the examples of synthetic polymers as follows:

- Poly D (Latide) (PLA)
- Poly (3-hydroxy butyrate) (PHB)
- Poly (Caprolactone) (PCL)
- Poly (3-hydroxy butyrate co-3 hydroxy hexanoate) (PHBHH)
- Poly (hydroxyalkanoates) (PHA5)
- Poly D (Latide-co-glycoside) (PLGA)
- Poly (3-hydroxy butyrate co-4 hydroxybutyrate) (PHB4HB)
- Poly [(1,3-bis-carboxyphenoxy propane)-co-(sebacic anhydride)]

SEMISYNTHETIC

These are prepared from natural material by means of chemical synthesis, thus consists of mixture of natural and synthetic substances. The example such as cellulose nitrate, cellulose triacetate, etc… [17].

BRAIN DISORDERS AND DRUG USED FOR TREATMENT

ALZHIEMER'S DISEASE

Alzheimer disease is the one of the progressive neurodegenerative disease caused by brain cell death, which leads to destroy memory and other important functions. In Alzheimer's the total brain size gets shrinks. In case of AD the lining of brain get affected, and the fewer nerve cells and its connections is lost, postmortem\autopsy will shows tiny inclusion in the nerve tissues is called as plaque or tangles.

Alzheimer disease is the most well-known reason for dementia. The term dementia depicts the loss of mental capacity related with steady demise of cerebrum cells. In overall World about1 in 8 peoples were affected by AD of age above 65. Women's are mostly affected by AD than men. There is an evidence that the people with BP and high cholesterol has a greater chance of getting AD. The age is the major risk for AD [18,19].

The nerve cells in the brain get tangles called neurofibrillary tangles, the protein depositedin the brain called beta amyloid plaques. The drugs such as cholinesterase inhibitor used such as DONEPEZIL, RIVASTIGMINE, and TACRINE were used.

DONEPEZIL

Donepezil hydrochloride is belongs to the group of acetylcholinesterase inhibitor. It action includes slow down the breakdown of neurotransmitter called acetylcholine in the brain. The neurotransmitter is the chemical substances which are stored in the nerve cells in the brain and the nervous system, and which transfer the message from one nerve cells to the other. They are basic essential for the normal functioning of brain and nervous system. The acetylcholine is broken by a chemical enzyme called acetylcholinesterase, which hydrolyze them to acetyl and choline. Donepezil, which increases the acetylcholine level in the brain. Thus it prevent the acetylcholinesterase action, thus it slows the breakdown of Ach, released from the remaining nerve cells which are undamaged nerve cells in brain.

This leads to the result of increasing the Ach in the brain. This improves the cognitive process of thinking, learning, and memory and improve the symptoms of dementia [20].

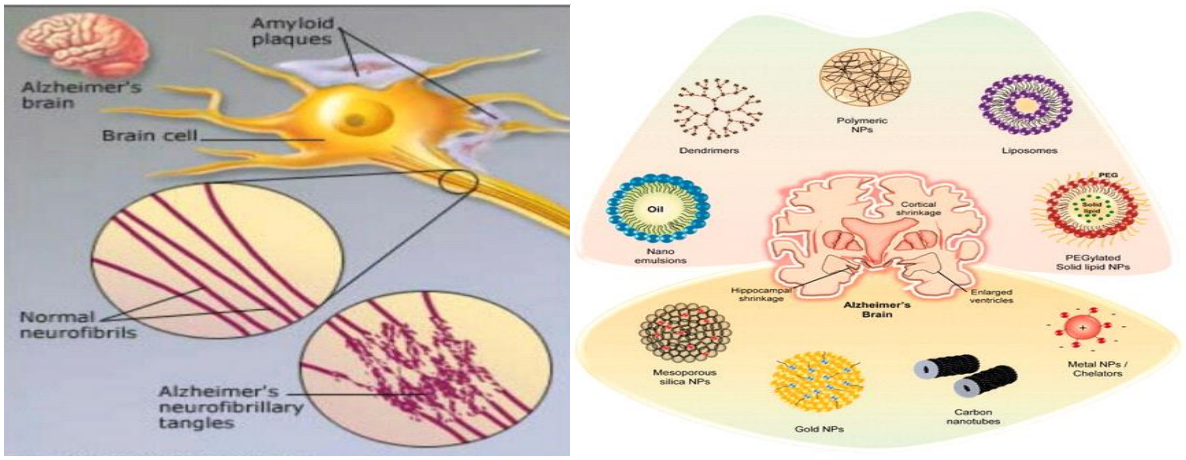

Fig 3: Alzheimer's Brain

PARKINSON'S DISEASE

Parkinson's disease is the one of the progressive degenerative disorder, mostly affecting older people. The signs includes, tremor, slower movement, muscle stiffness may occur. Parkinson disease is the one, in which the certain brain nerve cells become breakdown gradually or die. The Parkinson is due to an decrease in the level of dopamine in brain. The decrease in the dopamine leads to an abnormal activity of brain and subsequently there will be an increase in the acetylcholine level [22, 23].

About 10 million people were affected by Parkinson disease in the world approximately. The most consistent of PD is neuronal degeneration in the substantia Nigra , nigrostriatal tract and pars Compacta. This results in dopamine deficiency in the striatum, that controls the muscle coordinate movements and maintain the muscle tone [24].

CARBIDOPA-LEVODOPA

The Parkinson disease is due to a decrease level of dopamine in the brain. The dopamine itself does not pass the brain barrierbut levodopa may cross the BBB. The carbidopa is the drug that prevent the decarboxylation of levodopa, they are belongs to the class of decarboxylase inhibitor but the carbidopa cannot passes the BBB

It is the most effective medication in treating Parkinson disease, they may pass through the brain and changes its chemical structure as dopamine. The carbidopa prevent the decarboxylation of levodopa and prevent the levodopa conversion into dopamine outside the brain. Thus prevents the effect of nausea. It can be also used in the form of combination with benseraside [25].

MAO-B INHIBITOR

It includes rasagiline and selegiline, this may prevent the breakdown of dopamine in brain by inhibiting the monoamine oxidase B enzyme. The enzyme

metabolizes the dopamine in brain. The selegiline has two isoenzyme forms such as MOA-A and MOA-B; both were present in the peripheral adrenergic structure and intestinal mucosa. Which was later predominant in the brain and the blood platelets. The selrgiline are short lived, and they alone have a mind antiparkinsonian action.

The rasagiline MAO-B inhibitor with selegiline like therapeutic effect in parkinsonism, but it is 5 times more potent, longer acting and not metabolized to amphetamine. Therefore the dose is given about 1mg OD in morning[26].

CONCLUSION

For the treatment of brain disorder, the drug should pass through the BBB. Thus the particle should be nanometer in range. The particle size should be ranging from 1 to 1000nm. The drug should have the ability to target particular organ or tissue. It should have the properties of hydrophobicity and lipophilicity, since the brain is lipophilic in nature. The drug should made up of biocompatible and biodegradable polymer for controlled drug release.

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