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TARGETED DRUG DELIVERY ACROSS BLOOD-BRAIN-BARRIER EMPLOYING NATURAL NANOCARRIERS

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ABSTRACT
The central nervous system (CNS) of the body is protected by blood brain barrier (BBB). BBB is a highly complex structure that precludes the delivery of drugs to the brain, thus preventing the treatment in a number of diseases. One of the more significant reasons for the difficulty in treating brain diseases concerns the problems faced by many drugs when crossing the BBB. The barrier is formed by endothelial cells which are connected to each other at "tight" junctions that create a complete seal between them. Consequently, only lipophilic molecules are able to cross the barrier. Hydrophilic substances, in contrast, are unable to cross the lipid walls unless associated with a specific transporter. The inability of active agents to cross the barrier effectively means that those agents will not accumulate in adequate concentrations unless large doses are administered, doses that can have significant toxic side effects in other tissues. Establishing new therapeutic approaches to the treatment of cerebral diseases such as stroke, Alzheimer's disease or brain cancers has to address this issue of crossing the BBB. Moreover recent studies evidence the involvement of the BBB and especially the brain endothelial cells in the pathological process for numerous brain diseases suggesting the necessity to develop specific targeting for these cells The efficiency of many drugs is restricted to their potential to reach the site of therapeutic action. In recent years, the use of nanotechnology has been considered as a valuable strategy to achieve drug delivery to the brain and nanoparticles are developed as potential drug carriers. Nanocarriers possess unique features due to their size, can encapsulate therapeutic dose of many drugs and can be functionalized with various ligands for tissue and cell targeting. Lately peptides have been described as potential ligands for achieving endothelial cells and more specifically BBB targeting of nanocarriers. But the biodegradability of these nanocarriers is a serious problem. Many naturally occurring biocompatible materials can be used as nanocarriers. This review is focused on nano drug delivery using biodegradable, nontoxic and inexpensive natural molecules like chitosan, gelatin and PLGA as carriers. Role of nanoparticle size, bulk material chemistry, and surface chemistry in crossing the BBB is also discussed.

KEY WORDS: BBB, drug delivery, biodegradable, nanoparticles.

Blood Brain Barrier (BBB): Brain is the only organ in the body having its self guarding system called the Blood- Brain barrier (Fig.1 ref. Wikipedia images). BBB is an impermeable boundary between brain and blood stream (Fig. 2 ref. Wikipedia images). This net work of blood vessels allows the entry of essential nutrients while blocking all other materials. Thus it is acting as a protective barrier in order to keep the environment in the brain safe. Thus the toxins and other contagious materials floating around the brain cannot reach in it. For this aspect BBB is a blessing to brain because the brain is a very delicate organ and any infection could be destructing. But the curse is that these infectious components accumulate in the brain and destroying it eventually. Thus BBB goes both ways a blessing and a curse.

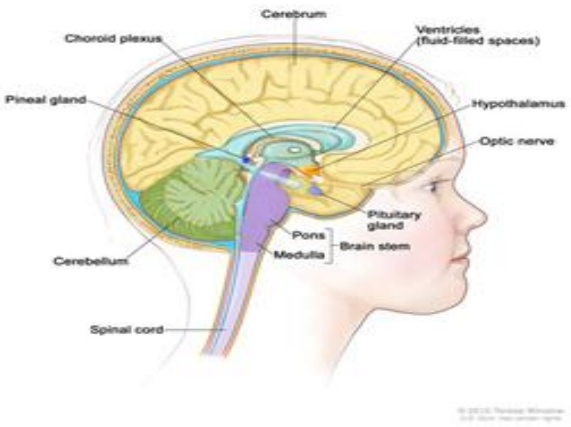

Figure 1 The structure of brain

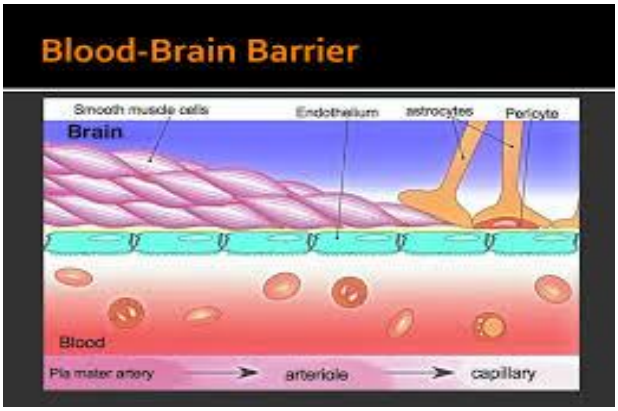

Figure 2 Blood brain barrier

Drug delivery to brain crossing BBB: The primary function of blood –brain barrier (BBB) is to protect the brain by preventing the entry of harmful toxins present in the blood stream into the brain.[1] Because of this BBB prevents the treatment in a number of brain diseases by blocking the delivery of drugs.[2] This action of BBB is attributed to its structure because usually in the body structure decide the function. The joints connecting endothelial cells are tightly packed preventing large molecules to pass between the junction spaces.

In order to enter the brain tissue the molecules must pass through the cell membranes of the endothelial cells. Only lipid soluble molecules are able to transverse the BBB.[3] Hydrophilic substances, in contrast, are unable to cross the lipid walls unless associated with a specific transporter. This raises the principal problem that we wish to address: the inability of active agents to cross the barrier effectively means that those agents will not accumulate in adequate concentrations unless large doses are administered, doses that even have significant toxic side effects in other tissues. Establishing new therapeutic approaches to the treatment of cerebral diseases such as stroke, Alzheimer's disease or brain cancers has to address this issue of crossing the BBB. Moreover recent studies evidence the involvement of the BBB and especially the brain endothelial cells in the pathological process for numerous brain diseases suggesting the necessity to develop specific targeting for these cells.[4] When the BBB is ruptured the brain is in the risk of infection and injury.

Criteria for effective drug delivery across BBB: Ideal drug delivery across BBB depend upon certain characteristics. The method should not damage the barrier and the drug carrier system should be non-toxic and biodegradable. The drug delivery should be selective and site specific. Controlled drug release should be possible by the method adopted and the therapeutic amount should be adequate for the desired time of action for its maximum action. Among the diverse methods obtainable for drug delivery nanotechnology based methods furnish best results for attaining these characteristics.

Nanotechnology in drug delivery: The effectiveness of a large number of drugs rely on their capacity to get into their scene of therapeutic activity. The development of nanoparticles that are capable of carrying the active agents into the brain (BBB and parenchyma) and to the diseased sites thus appears to be a promising approach.[5,6,7] Thus nanomedicine is emerging as a modern tool in targeted drug delivery. The drug is loaded into the nanoparticle and it can penetrate the BBB to attack the targeted molecule as illustrated in figure 3(Ref. Wikipedia images). Brain's immune system comprising of cells called microglia play a major role in drug delivery through BBB. These cells readily respond to changes in the surroundings of BBB and they can be activated to perform different functions and can play a key role in brain disease treatment. For the carriers to be effective in targeting the brain, their surfaces must be designed by decorating with specific ligands. Ligands as transferrin, glucose or specific antibodies have been proposed and linked to various types of nanoparticles (liposomes, polymeric or lipidic nanoparticles,….).[8] These approaches are based on the recognition of these ligands by receptors and transporters which are overexpressed by the brain endothelial cells allowing the transport of essential nutrients for brain tissue.[9] Numerous proofs of this concept have been published.[10. 11] For example, nanoparticles linked to an antibody directed against transferrin receptor have demonstrated their ability to reach the brain and to deliver an antiapoptotic peptide in brain for neuroprotection during an ischemia.[12]

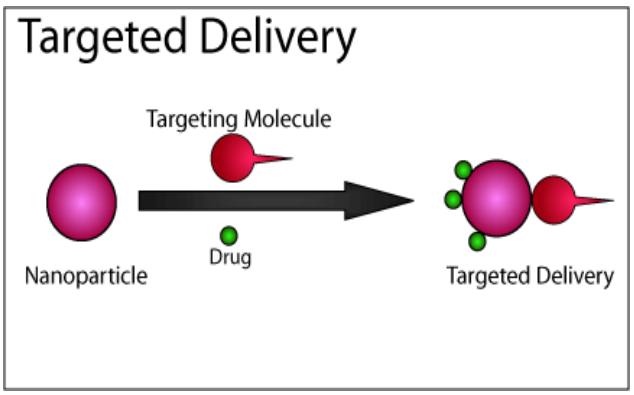

Figure 3 Nanoparticles in targeted drug delivery

Biodegradability of nanocarriers in drug delivery

The use of nanoparticles in medical field and drug delivery is a fast growing research field. But these carrier systems itself are hazardous to the patients. Proper disposal of these nanocarriers after the drug delivery is a serious problem. Thus these carriers itself is imposing potential threat to the patients.[13] The primary goals of nanobased drug delivery are site specificity, reduction in toxicity, biocompatibility and environment safety.[14] Thus the biodegradability of these nano drug carriers is a serious problem to be addressed. The drug delivery action of a biodegradable nanopartilce is demonstrated in figure 4 where the drug is preloaded into the particles

and once it reached the target, the polymer matrix eroded and the drug is released.

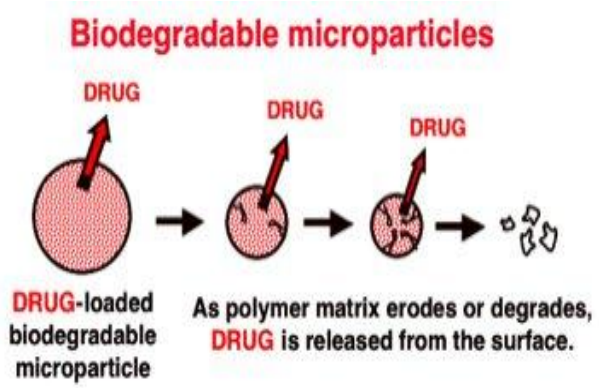

Figure 4 Drug delivery using biodegradable nanoparticles (Ref. Google images)

Natural nanocarriers

Biodegradable nanoparticles are getting greater attention because of their potential to perform as carriers for site specific delivery activities.[15] Natural polymers are widely used as naocarriers now because they occur abundantly in nature and thus makes it more economical. Natural products are efficient drug carriers not only because of their improved site specific action but they offer enhanced biocompatibility and can be used in much safer way.[16] Some naturally occurring biodegradable polymeric materials used as nanocarriers include Poly-D-L-lactide-co-glycolide (PLGA), Polylactic acid (PLA), chitosan and gelatin.

Preparation of polymeric nanoparticles

These can be prepared from proteins, polysaccharides and synthetic polymers. Nanomaterials and various polymers can be put together to develop right atmosphere not only to attach drugs but to identify the matching receptors on the brain cells. One desirable feature of polymers is that we can modulate them chemically. Their important basis for action is its site specific drug delivery.[17] It depends upon size of the prepared nanoparticles, properties of drug to be embedded in the polymer, drug release effect, degree of biodegradability and surface chemistry of the nanoparticles. Based upon these properties various biodegradable polymeric nanoparticles can be synthesized by reported procedure.[18]

Polylactic acid (PLA)

PLA is a biodegradable polyester molecule derived from sustainable sources like starch or sugar cane. This can easily breakdown into the biodegradable monomer lactic acid. It can be used as a support system because it can transfer the drug into the affected part and can undergo graduadegradation within the body in a short time.[19] PLA is a potential candidate in drug delivery applications because of its biodegradable nature and for the rapid arrangement of minute particles under proper conditions. But PLA based drug delivery suffer from low loading efficiency and low drug enclosing capacity.

Poly (lactic-*co*-glycolic acid) (PLGA)

PLGA is a biodegradable and biocompatible copolymer. It is obtained from two different monomers like the cyclic dimers of glyclolic and lactic acids. PLGA is an efficient biodegradable polyester because it undergoes hydrolysis in the body in presence of water to the monomers. Thus the toxicity associated with PLGA is eliminated and it can be successfully employed for drug delivery applications. PLGA is a copolymer formed from monomers of cyclic dimers, glycolic and lactic acid and obtained by the ring opening copolymerization. Catalysts used for this polymerization are either complexes of Tin (Sn) or aluminium isopropoxide and the monomers are linked together in PLGA by ester linkages.[20] PLGA is one of the most efficient biodegradable polymers as natural drug carrier because its ester linkage can easily break down in the body to produce biodegradable monomers lactic and glycolic acid.[21] These monomers are easily break down in the body and can be eliminated as carbon dioxide and water.[22] Thus the toxic effects of the drug carrier is greatly reduced.

Chitosan (CS)

Chitosan is a polysaccharide made up of glucosamines and N-acetylglucosamines. It can be useful to deliver drugs through skin. CS is obtained by extensive deacetylation of chitin present in the shells of crustaceans and mollusks.[23] Chitosan nanoparticle are widely used as natural drug carriers because of their less toxic and stable nature. It can be prepared and administered by simple routes. CS is soluble in slightly acidic water and thus for drug delivery applications organic solvents could be avoided. Thus hydrophilic drug molecules can be effectively encapsulated into CS nanoparticles. Also the positively charged. Chitosan particles could effectively target the negatively charged biological membranes.[24] The efficiency of Chitosan in drug delivery is also attributed to their metabolic degradation in the body. Chitosan also act as a diluents in drug delivery systems.[25] Because of low hydrophilicity and high crystalline nature of PLA its application in drug is delivery is limited because of the low degradation rate. But Chitosan can blend with PLA and can be effectively used for anti-HIV drug delivery applications.[26]

Gelatin

Gelatin is a mixture of peptides and proteins obtained from collagen by boiling. Collagen is the main protein found in the connective tissues of mammals. Gelatin easily dissolves in hot water making it an efficient biodegradable carrier in drug delivery and is widely used becaue of its low cost and availability of many active groups for binding to target molecule.[27] The drug molecule can be decorated with gelatin nanopartilces and can be administed nasely because of the biocompatible and biodegrable nature of gelatin. This way it can bypass the BBB and target the affected brain tissues. In order to increase the cell adhesion properties of PLGA, it can be emulsified as composities with gelatin. Alternatively PLGA and gelatin can be club together for controlled

drug delivery by electrospinning. This could lead to enhanced activity because of the increased surface to volume ratio of electrospun nanofibers.[28]

Nano particle size and surface modifications in crossing BBB

The blood brain barrier (BBB) is acting as a protective covering to the brain by blocking the entry of large molecules into it. But this characteristic prevents the treatment in a number of diseases by weakening the entry of drugs into brain. The efficiency of therapeutics to pass into the BBB mainly depends on the size of particles and majority of these agents could not cross the BBB. In order to treat brain diseases it is highly important to find the mechanism by which these drug molecules cross the barrier. In recent years, nanoparticles appear a valuable strategy to achieve drug delivery to the brain. Nanomaterials increase the period of drug circulation in the blood. But the space between brain cells is viscous and it is difficult for the large particles to move through it. This control the entry of large particles into the brain cells by crossing the BBB. This problem can be adjusted by modifying the surface of the nanoparticles to improve the duration of drug circulation in blood.[29]

The size, coating and the charges present on the surface have a profound effect on the ability of nanoparticles to cross the BBB. There are many ways to stabilize the nanoparticles and to increase their ability to cross the BBB. This includes attaching suitable linkers or by increasing the particle size by combining small nanoparticles. One such way to increase the particle size is to thickly coat the particle surface with polyethylene glycol (PEG). This strategy increased the particle size, reduced its sticking to the brain cells and also prevented the clustering of small particles. The biodegradable PLGA nanoparticles can be coated with small peptides to improve its passage across BBB is also reported.[30]

CONCLUSION

Delivery of drugs for the treatment of brain diseases is limited because of the hindrance by BBB. Nanoparticles emerged as a valuable choice as potential drug carriers. Nanomedicine is acting like a molecular Trojan horse which can sneak drugs across the barrier. For therapeutic molecules which could accelerate along with the lipophilic medium or diffuse through it, optional paths of BBB entry have to be explored. Attaching the drug molecule to the nano carrier catalyze its transportation by tricking the BBB through this Trojan horse approach. To fully exploit this approach, development of biodegradable nanocarriers, their stabilization and effective crossing of BBB need to be investigated further.

CONFLICT OF INTERESTS

The author declares that there is no conflict of interests regarding the publication of this paper.

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