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Review Article

Nanoparticles for Brain Targeting

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ABSTRACT

Nanoparticles are solid colloidal particles ranging in size from 1 to 1000 nm that are utilized as drug delivery agents. The blood brain barrier represents an insurmountable obstacle for a large number of drugs including antibiotics, anti neoplastics and a variety of CNS active drugs especially neuropeptides. One of the possibilities to overcome this barrier is a drug delivery to brain using nanoparticles. The use of nanoparticles to deliver drugs to the brain across the blood brain barrier may provide a significant advantage to current strategies. The primary advantage of nanoparticles carrier technology is that nanoparticles mask the blood brain barrier limiting the characteristics of the therapeutics, drug molecules and it also decreasing peripheral toxicity by causing slow drug release in the brain. The nanoparticles may be especially helpful for the treatment of the disseminated and very aggressive brain tumors. The mechanism of nanopraticles mediated transport of drugs is mostly endocytosis by endothelial cells lining the brain blood capillaries. Physiological factors such as phagocytic activity of reticulo endothelial system and opsonization may limit the amount of brain delivered drug.

INTRODUCTION

Nanotechnology is the creation of useful materials, devices and systems through the manipulation of such miniscale matter; nanoparticulate system has gained increasing interest within therapeutics [1]. Due to their low toxicity they are good candidates for targeting tissues and cells with different compounds.

The treatment of brain cancers is limited by the inadequacy in delivering therapeutic agents in such a way that drug molecules reach the desired targets. In order to achieve efficient treatment of central nervous system cancers, it is necessary to transport therapeutic agents across the specialized vascular system of the brain, the blood-brain barrier which can present formidable challenges.

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The blood-brain barrier (BBB) and brain cancers: Therapeutic options and problems

The BBB is a system of vascular cellular structures, mainly represented by tight junctions between endothelial cells, and an ensemble of enzymes, receptors, transporters, and efflux pumps of the multidrug resistance (MDR) pathway (reviewed in references-[2,3,4,5,6,7,8]) that control and limit the access of molecules to the brain, either by paracellular or transcellular pathways. Since the vascular density in the brain is very high, once molecules have penetrated the BBB, they distribute rapidly to the whole brain tissue. A few lipid-soluble molecules are able to pass freely by passive diffusion from the blood to the interstitium of the brain, whereas ionic solutes are unable to do so. Chemical modification of drugs that enhance lipophilicity results in an increased distribution of drug in all organs. The design of carriers that cross the BBB at sites is defined by the properties of the vasculature at that specific localization, using biology-based strategies to target specific transport system at the BBB must be designed. These carriers may consist of drugs or polymeric

nanocarriers chemically modified with recognition and transcytosis-enhancing ligands that can allow the release of the active free drug, once transendothelial transport has been performed. Functionalized drugs must structurally resemble the normal transport substrates making them recognizable by the transporter; however, maintaining the biological activity of the drug is another challenge. Various transport systems are shown in Figure 1.

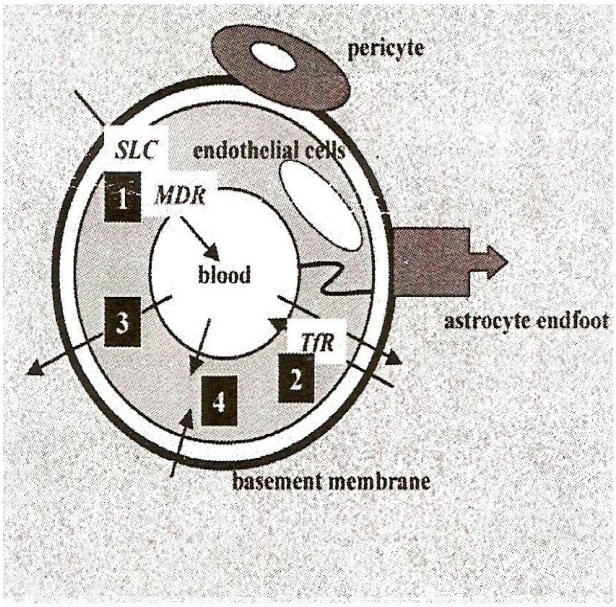

Figure 1: Various transport systems across the brain

NATURE OF NANO PARTICLES:

Nanoparticles are polymeric solid colloidal particles ranging in size from 10-100 nm and are employed to carry the drugs through absorption or incorporation [9, 10]. The various size range of nanoparticles and their characters along with uses are shown in Table-1.

Drugs targeting brain cancers across the BBB: chemical functionalization of therapeutic agents or of nanoparticulate carriers:

The limiting factor in the treatment of brain cancers is the delivery of therapeutic agents to the brain across the BBB [6]. A very restricted number of lipid soluble small molecules (MW<400Da) cross the BBB by free diffusion. All the other molecules must use specific system to be transported across the BBB. Therefore, the future for treatment of malignant brain cancers relies on the development of therapies targeting the markers and transporters of the tumor-associated cerebral endothelium, not only at the primary tumor sites but also at the invasive areas. Biological targeting involves that a specific marker (a target) is selectively expressed or is expressed on disease-associated cells at a much higher level than on normal cells. The targeting agents may be antibodies directed toward an antigen residing on the target tissue or ligands for receptors or transporters, and may be covalently conjugated via an appropriate chemical bond either directly to the drug or to a vector, such as a nanoparticulate device. Most of the targets identified and evaluated until now for brain cancer have been related to molecules associated with enhanced angiogenesis or increased nutrient demand of the tumors.

Some drugs have conjugated to ligands or antibodies, or have been incorporated into carriers bearing ligands or antibodies for recognition by cell surface receptors expressed by target cells. Major obstacles include the physiological stability of these structures and their transport across biological barriers, in particular the blood-brain barriers, for the delivery of therapeutic drugs. In addition, for maximal efficacy, drugs must reach their targets in the appropriate location within tumor cells, that is, the cytosol, cell organelles, or the nucleus or transferrin conjugate represent potential transport system to the brain [11,12,13].

TYPES OF DRUGS THAT ENTER THE BRAIN:

Brain allows only the drugs having o/w partition coefficient, high lipid solubility and diffuse them passively. In the disease condition like tumors antibiotics such as pencillins which are polar, water soluble and ionized at plasma pH can easily pass due to disruption of blood brain barrier.

Three different approaches have been utilized successfully to promote crossing BBB by drugs.

1. Use of permeation enhancers such as dimethyl sulfoxide (DMSO).
2. Osmotic disruption of the BBB by infusing carotid artery with manntiol.
3. Use of dihydropyridine redox system as drug carrier to the brain.
4. The lipid soluble dihydropyridine is linked as a carrier to the polar drug to from a prodrug that readily crosses the BBB.

Table 1: size range of nanoparticles and their characters along with uses

Size range of nanoparticles	Characteristics	Uses
Nano particles in the range of 50-100 nm	Larger particles cannot enter tumor pores while nanoparticles can easily move into a tumor	Cancer treatment
Nanosizing in the range of 100-200 nm	Low solubility	More effective treatment with existing drugs
Polymers	These molecules can be engineered to a high degree of accuracy	Nanobiological drug carrying devices
Nanocapsules	Evading body`s immune system whilst directing a therapeutic agent to the desired site.	A Buckyball- based AIDS treatment is just about to enter clinical trials
Nanoporous materials	Evading body`s immune system Whilst directing a therapeutic agent to the desired site.	When coupled to sensors, drug delivering implants could be developed.
Pharmacy on a chip	Monitor conditions and act as an artificial means of regulating and maintaining the body`s own hormonal balance	Diabetes treatment

Table 2: Chemotherapeutic agents and transports across the brain

Name	Characteristics	Transport across the BBB
Doxorubicin	Anthracyclins inhibits nucleic acid synthesis very narrow therapeutic index	No
Paclitaxel	Microtubule-stabilizing	No
Cisplatin	Inorganic Platinum ion complexes DNA alkylating and intercalating, short half life	No
Iirinotecan	Inhibits DNA topo isomerase I induces single strand DNA lesions	Yes
Methotrexate	Anti metabolite of folic acid inhibits dihydro folate reductase and DNA, RNA and protein synthesis	No
Carmustine	Alkylating agent	No

Prospects accounted for the enhanced delivery of drugs to the brain using nanoparticles are [17, 18, 19, 20]

Higher concentration gradient at the blood brain barrier that may enhance the transport across the endothelial cell layer and hence, increased retention in the brain. Solubilization of endothelial cell membrane lipids by surfactant action of nanoparticles leading to membrane fluidization and enhanced drug permeability to BBB. Loosening of tight junctions between endothelial cells and increased permeability of drug or drug-nanoparticles conjugates through these channels. Endocytosis of the drug intracellulary takes place and transcytosis of the drug bound nanoparticles through the endothelial cell layer also takes place.

POLYMERIC NANOPARTICLES:

The advantage of using polymeric nanoparticles (PNP) in drug delivery are many, the most important being that they generally increases the stability of any volatile pharmaceutical agents and it can be easily and cheaply fabricated in large quantities by a multitude of methods. Additionally, the use of absorbable or degradable polymers such as polyesters provides a high degree of biocompatibility for PNP delivery system. This is an essential feature for such potential applications as tissue engineering, which will be briefly discussed later. Furthermore, the use of PNP allows for the design of individual delivery systems for highly specific applications. Among the adaptations that can be made are surface modifications of the polymer, use of different fabrication methods, selection of a variety of pre-existing polymers or copolymers, and formulation of novel polymeric

materials [4]. The last possibility is especially exciting, as it may be possible in the future to design specific PNP delivery systems for individuals.

Polymeric nanoparticles have the potential to completely transform drug delivery technology. PNP's represented a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness. Also, PNP`s can have engineered specificity, allowing them to deliver a higher concentration of pharmaceutical agent to a desired location. This feature makes PNP as ideal candidates for cancer therapy, delivery of vaccines, and delivery of targeted antibiotics. Polymeric nanoparticles are the future of drug delivery technology and represent the best way to increase specificity in pharmaceutical therapy, a key to defeating cancer. Typical formulation methods to produce particles of various shapes and sizes [5]. Figure 2 shows the representative photograph of nanoparticles.

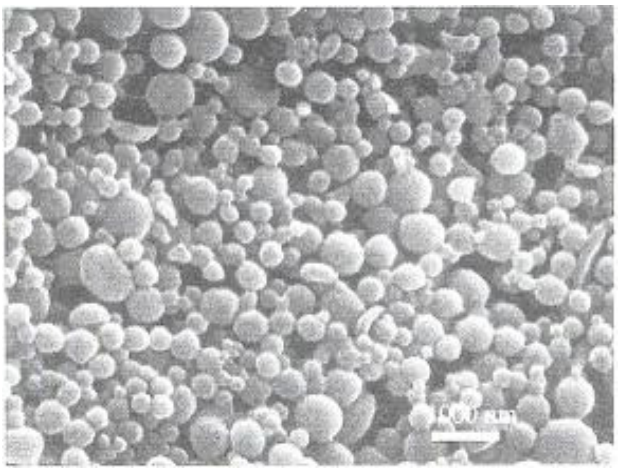

Figure 2: A representative photograph of nanoparticles

Chitosan nanoparticles:

Chitosan nanoparticles have been reported to extend circulation time in the blood and decreased uptake by the reticuloendothelial system. Nanoparticles coated with polysorbate 80, hold great promise for transport of agents across BBB [9,14,15]. Polysorbate 80 coated chitosan nanoparticles are efficient as brain delivery carriers [16].

Chitosan nanoparticles are prepared by ionic cross linking of chitosan solution (with or without drug) with TPP prepared in presence of Tween 80 as a resuspending agent to prevent particle aggregation, at ambient temperature while stirring.

Quantum dots for Brain tumor Diagnosis: [21, 22, 23, 24, 25]

The intra operative diagnosis of brain tumor and the timely evaluation of biomarkers that can guide therapy are hindered by the paucity of rapid adjunctive studies. This study evaluates the feasibility and specificity of using quantum dot-labeled antibodies for rapid visualization of epidermal growth factor receptor (EGFR) expression in human brain tumor cells and in surgical frozen section slides of glioma tissue. Steptavidin-coated quantum dots (QD`s) were conjugated to anti-EGFR antibodies and incubated with target cultured tumor cells and tissues. The experiments were conducted first in human glioma tumor cell lines with elevated levels of EGFR expression (SKMG-3, U87) and then frozen tissue section of glioblastoma multiforms and of oligo dendro glioma. The bioconjugated QD`s used in the study were found to bind selectively to brain tumor cells expressing EGFR. QD complexed quickly to the cell membrane (less than 15min), and binding was highly specific and depended on the expression level of EGFR on the cell membrane. Tissue experiments showed that only tumor specimens expressing EGFR were labeled in less than 30min by QD complexes. These findings demonstrate that QD-labeled antibodies can provide a quick and accurate method for characterizing the presence or absence of a specific predictive biomarker.

Surface modification: [28, 29, 30, 31, 32]

The modification of the surface of nanoparticles by using various polymers and targeting materials helps in increasing of electrostatics intervention between the drugs and binding sites of the targeted tissues and thus leads to the better targeting of the nanoparticles loaded with drug to the target site. For e.g.: Magnetic nanoparticles, iron oxide nanoparticles (IOP`s) covered with a layer of biodegradable polymers shell or evenly distributed in the matrix of polymer nanoparticles have been reported to be effective magnetic drug carrier [29, 30, 31]. The polymer coating have found to reduce aggregation problem of uncoated IOP`s and lower toxicity. Such composites have been used to successfully deliver DNA, RNA, and other relatively small therapeutic molecules to target tissues by the use of external magnetic field.

Surface coating of iop`s and characterization: [26-32]

The IOPs were synthesized by co-precipitation of the ferrous and ferric chloride solution in concentrated sodium hydroxide solution as reported earlier. In this experiment a stock solution of ferrous and ferric chloride having Fe^{2+}/Fe^{3+} ion in the ratio equal to 0.5 was prepared by dissolving required amount of the corresponding salts and same stock solution was used to precipitate IOP`s. Briefly, 1M NaOH and 12ml gelatin solution (A or B, 5% (W/V), pH 5) were added to the ferrous and ferric chloride stock solution (0.5, 1 and 2ml), simultaneously. The resulting black precipitates were redispersed in 12ml of deionized water with brief sonication and dialyzed against deionized water overnight. The homogenous dispersions of surface-coated IOP`s were collected by removing the aggregates by centrifugation at 3000rpm for 2min. The product would be referred to as GIOIBPs-0.5, GIOIBPs-1 and GIOIBPs-2 for gelatin B-coated IOP`s and GIOIAPs-1, and GIOIAPs-2 for gelatin A-coated IOP`s. The number in each of the name represents the corresponding volume of ferrous and ferric chloride solution used for the precipitation.

CONCLUSION

A few strategies exist to enhance transport of anti-cancer agents across the BBB for the treatment of high-grade brain tumor:

I. Passive permeation of lipidated drugs, however, this strategy is possible only for small molecules
II. The development of pro-drugs hijacking the transport mechanisms at the BBB, however, the high selectivity of these transport mechanisms limits this approach
III. The development of drug-loaded nanocarriers able to take advantage of any disruption of the BBB at tumor sites. The most promising tools to deliver therapeutic drugs to tumors of the brain may be nanoparticles [14, 15]. Colloidal system, such as nanoparticles show promise for brain targeting, enhanced by the ability to modify their properties, increasing drug efficacy and attenuating side effects. Technical problems associated with developing targeted nanoparticles include the increased complexity of the nanoparticles, as well as the increased risks of adverse reactions, while advantage include the increase in drug reaching its target, enhanced selectively, and the potential for delivery of multiple agents at the same site[14]. Creating a toolbox of molecules that can be assembled hierarchically into ordered structures, spatially and chemically controlled is however, essential to make nanoparticles an attractive and efficient means of encapsulating and delivering drugs to the CNS tumor. Thus, an ideal theoretical therapeutics-delivery nanoparticle system for brain cancer would be one that:

i. Selectively targets diseased BBB
ii. Bears an inhibitor of the efflux pump linked by a locally hydrolysable bond, and
iii. Transports drugs across the cerebral vasculature and delivers them to their target, which is the brain cancer cell. Challenges yet to overcome include identification of disease-associated changes of the BBB properties in brain cancers and the modification of drugs or drug-carriers with targeting and transport-enhancing agents. There will be plenty of possibilities to be explored; in the near future however, in my opinion, the most promising vectors are those involving small molecules as BBB targeting/transport-enhancing agents, stable in biological media and versatile for synthesis purposes, and to carry a large drug payload.

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