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USE OF LIPOSOMES AND NANOPARTICLES FOR BRAIN DRUG TARGETING

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ABSTRACT
The Blood Brain Barrier (BBB) poses a obstacle for a drugs, including antineoplastic agent, antibiotics, neuropeptides, CNS active agents, to be delivered to the brain for therapeutic reasons. The use of formulation dependent strategy such as the use of heterogenous pharmaceutical systems for its effective targeting to the brain is being explored recently. Liposomes and Nanoparticles are good possibilities to achieve the goal. Chemically modified liposomes and nanoparticles are tried in recent times to act as brain targeting aids, and this article tries to explain the possibilities and problems behind such an endeavor.
KEY WORDS: Liposome, Nanoparticle, Phospholipid, PEG Polymer, Blood Brain Barrier, Drug targeting, CNS.

INTRODUCTION

In the 20th century, drug development for the brain & other organs, was dependent on a chemical basis, creating small molecules pharmaceuticals, having a molecular weight of approximately 500 Daltons. In the recent century, the CNS drug development will be biology driven, bringing in focus the delivery of large molecule pharmaceuticals, such as antisense drugs, antibiotics and recombinant proteins. But due to absence of functional platform for CNS drug targeting science, the large molecule pharmaceutical cannot be delivered to brain, and hence the full therapeutic advantage of such agents will not be utilized properly.

The brain drug targeting in recent times has shown advances in the field of direct invasive delivery, lipid mediated transport, carrier mediated transport of small molecules, receptor mediated transcytosis of peptides, peptide radio pharmaceuticals, biological linkers, genetic vectors, protein neurotherapeutics and antisense neurotherapeutics[1].

An effective approach to the modification of formulation strategies in the making of liposomes and nanoparticles, and their area of applications, are discussed.

APPLICATION OF LIPOSOMES

Liposomes are considered as one of the optimal drug carrier system, not only they are biodegradable and easy to prepare, but also they have remarkable versality in terms of composition, size and other structural characteristics. Liposomes are microscopic vesicles composed of one or several lipid membranes surrounding discrete aqueous compartments. These vesicles can encapsulated water soluble drugs in their aqueous spaces and lipid soluble drug within the membrane itself. Liposomes are inherently targeted to liver and spleen. When the drug encapsulated liposomes are introduced into the blood stream, the body's defense system considers them as foreign particles and an antigenic opsonization reaction follow. The behavior of drug in vivo can often be changed in dramatic fashion by coupling the drug to carrier moiety.

The pharmaco-dynamic behavior leads to better therapeutic index of the drug. The inherent efficiency of CNS drug development is increased by incorporating structure transport relationship (STR) during the formulation development phase. Drugs may be incorporated in either Small Unilamellar Vesicles (SUV), having diameter of 40-80 nm, or Multivesicular liposomes (MLV) having a diameter of 0.3-2 microns. Liposomes are essentially lipophilic "sacks" for the delivery of drug through the BBB using the encapsulation method of the drug. But drugs that have a molecular weight in excess of 400-600 Dalton threshold have restricted BBB transport. The peripheral administration of MLVs showed an accumulation in brain, but it was hypothesized as an embolism phenomenon in the brain microvasculature, which has a diameter of 0.3-2 microns. In the same experiment, the SUVs of 40-80 nm diameters could not cross the BBB.(Gennuso et al, 1993). The encapsulation of super oxide dismutase (SOD) in liposomes was found to promote increased CNS pharmacological activity of the enzyme in vivo, but this was achieved by doing this experiment in traumatic brain-injury model causing disruption of BBB. (Chan et al, 1987)[2].

Liposomes do not cross BBB, it is possible to formulate immunoliposomes which can cross the BBB via the receptor mediated transcytosis (RMT). The construction of immunoliposomes involves covalent conjugation of specific monoclonal antibodies (Mabs) to the surface of the liposomes. The rapid plasma clearance of liposomes or immunoliposomes can be prevented by the conjugation of PEG polymers to the surface of liposomes.(Papahadjopoulos et al, 1991). This gives formation to "hairy" liposomes where the extended PEG polymers minimize the absorption of plasma proteins to liposome surface.

RECENT TRENDS IN LIPOSOME APPLICATIONS

Liposomes find it way for the targeted drug delivery for brain cancer treatment. Examples of biodistribution studies showed results for several murine tumors, human tumor xenografts inoculated by various routes, including a brain implanted tumor. Liposome localization in tumors in brain and in other organs may be due to a result of an enhanced rate of extravasations through the abnormally permeable microvasculature of tumors coupled with an impaired lymphatic drainage. These results stress the potential of such long circulating liposomes with some targeting properties, to manipulate the pharmacokinetics of anticancer drugs and enhance drug delivery to brain tumors. This therapeutic approach has been validated in AIDs related Kaposi's

sarcoma and presently being tested for various types of solid tumors[3].

Adenosine Tri Phosphate (ATP) can be supplied to brain, which has got a potential application in human resuscitation from deep brain hypogeric states. This is done in an experiment by administering intracerebroventricularly and intracarotidally to rats subjected to brain ischaemic episodes by clamping of carotid arteries and lowering of systemic blood pressure. It was seen that when entrapped in liposomes, ATP greatly increased the number of ischaemic episodes before brain electrical silence and death[4].

In spinal chords, the immunoliposomes appear to penetrate a substantial distance, transfecting neurons several centimeters from the site of delivery. This is a promising data to provide an effective transfection system for gene delivery in CNS, the liposomes were constructed with N-glutaryl-phosphatidyl-ethanolamine conjugated antibodies and a beta galactosidase plasmid under the control of cytomegalovirus promoter[5].

Administration of the AZT by gavage to rats indicated poor bioavailability consistent with the acid labiality of AZT-CDS. The administration of AZT-CDS in dimethyl sulfoxide (DMSO) intraintestinally did not result in brain levels of AZT. Use of a liposome formulation was, however, did provide for significant uptake with administration to jejunum more effective than AZT-CDS administration to the ileum or colo-caecum. These results suggest that a liposome formulation in an enteric coated AZT-CDS tablet may provide for pharmacologically useful oral bioavailability[6].

Vector mediated drug delivery to brain employs the chimeric peptide technology, wherein the nontransportable drug is conjugated to BBB vector. Multiple classes of therapeutics can be delivered to brain with the chimeric peptide technology, including peptide based pharmaceuticals, such as vasoactive intestinal peptide analog or neurotrophins such as brain derived neurotropic factor, anti sense therapeutics and small molecules incorporates in liposomes[7].

Usage of cationic liposomes complex for in vivo gene transfer into adult mammalian central nervous system by continuous injection of plasmid DNA shows an improvement over previously applied liposome mediated direct in vivo gene transfer, especially when using highly differentiated, quiescent cells of the adult mammalian CNS. This new techniques may be able to a wider application of liposome mediated gene transfer technology not only to basic analysis of gene functions in the brain but also for clinical treatment of certain CNS disorders[8].

APPLICATION OF NANOPARTICLES

Generally nanoparticles have a diameter in the 100-400 nm ranges and are comprised of biodegradable polymers. Like liposomes, nanoparticles are rapidly cleared from blood following i.v. administration and above 90% of the nanoparticles are removed from the blood stream within a very short time. PEG polymers ranging from 5-20 Kilo Dalton in molecular weight are co-valently conjugated to surface of nanoparticles.

In an experiment, analgesia was induced in mice following the i.v. administration of opoid particle, at a dose of 7.5 mg/kg using 230 nm nanoparticles, (Kreuter et al, 1995). This was an unexpected phenomenon because 230 nm-sized nanoparticles would have been expected to get blocked by BBB, since 40-80 nm liposomes do not cross BBB. The nanoparticles were stabilized using stabilizing agents, such as polysorbate 80, also known an Tween 80. Detergents can cause solvent mediated BBB disruption.it is necessary to administer relatively large doses of polysorbate 80, up to 200 mg/kg, intravenously to stabilize the nanoparticles. Recent studies show that this detergent present in formulation is responsible for enhanced BBB transport of drug/nanoparticle/Tween 80 complex. So, nanoparticles, like liposomes, do not cross BBB in the absence of a parallel use of a BBB disruption strategy[9].

RECENT TRENDS IN NANOPARTICLE APPLICATIONS

PEGylated polymeric nanoparticles are presented as a potential efficient drug carrier for the delivery of active therapeutic molecules in prion experimental diseases. PEGylated nanoparticles show a higher uptake by brainand spleen that are both target tissues of prion particle accumulation in scrapie-infected animals[10].

Usage of colloidal polymer particles in a nanoparticle formulation has been tried for the passage of peptides through the BBB. The formulation consisted of dalargin bound to polymer (butyl cyanoacrylate) nanoparticles by sorption, coated with polysorbate 80. i.v. injection of this formulation to mice resulted in analgesic effect. All controls, including a simple mixture of 3 components, drugs, nanoparticles and surfactants, mixed directly before i.v. injection, exhibited no effect. Analgesia was also prevented by pretreatment with naloxone. Fluorescent and electron microscopic studies that the passage of particle bound by phagocytic uptake of polysorbate 80 coated nanoparticles by the brain blood vessel endothelial cells[11].

Nanoparticles can be administered orally to deliver AZT. Hexacyanoacrylate nanoparticles were used as colloidal drug carriers for AZT. The area under curve (AUC) for treated nanoparticles in blood and brain were found to be higher by 30% than the control, which were labeled with 14 C radioactive tracers. The results indicate that nanoparticles are a promising drug targeting system for nucleoside analogues. Also, the increase in drug availability at sites e.g., in the blood and in the brain, may allow a reduction in dosage and a decrease in systemic toxicity[12].

Use of Solid Lipid Nanoparticles (SLN) loaded with tobramycin was able to pass BBB in rats to a greater extent after i.v. injection than after duodenal administration. In this experiment SLN were prepared and administered by duodenal and i.v. routes to rats and tissues distribution were noticed and compared to those of tobramycin solution after i.v. administration. The tissue distribution between tobramycin loaded SLN administered duodenally and i.v.was different. In particular, the amounts of tobramycin in the kidneys after tobramycin loaded SLN administration either duodenally or i.v. was lower than after administration of i.v. solution. On the whole, SLN proved to be better method to distribute the drug to the brain[13].

Different types of surfactants can also be used to study the comparing effects and advantages of one over the other. The leu-enkephalin analog hexapeptide dalargin was bound to polybutylcyanoacrylate nanoparticles by sorption. Different surfactants were coated over these nanoparticles and were injected i.v. to the mice. Only nanoparticles coated with polysorbate 20, 40, 60 & 80 yielded a significant effect. The highest effect was observed with polysorbate 80. Maximum effect were found after 15 min, at a dalargin dosage of 10 mg/kg, and after 45 min, with 7.5 mg/kg[14].

CONCLUSION

Liposomes are now used commercially as cosmeteuticals and more importantly as pharmaceuticals. Three major achievements of liposome application are remote loading of drug by pH, ion gradients steric stabilization, and lipoplexes based on complexes of cationic liposomes with anionic nucleic acid or proteins extended avenues of new research towards novel use of liposomes and a large spectrum of product[15].

The recent trends although show a mixture of promise and drawbacks, it is the latter that demands more rigorous research in the development of liposomes as targeted delivery dosage forms, especially to brain.

The drugs that have successfully able to cross the BBB using this career had been hexapeptide dalargin, the dipeptide kytorphin, loperamide, tubocurarine, the NMDA receptor antagonist MRZ 2/576, and doxorubicin[16]. The nanoparticles are especially helpful for the treatment of disseminated and very aggressive brain tumors. Nanoparticles mediated transport to the brain depends on the overcoating of the particles with polysorbates, especially with polysorbate 80.

REFERENCES

1. Pilar, C., Bruno, G., Irene, B., Corinne, L., Jean-Philippe, D., Alun, W., Jean P. A., Dominique, D., and Patrick, C., PEGylated Polycyanoacrylate nanoparticles as vector for drug delivery in prion diseases, *Journal of Neuroscience methods*, 2001; 111: 151-155.
2. William M. Pardridge, Brain drug Targeting, Future of brain drug development, Cambridge University press, 2001; 49-51.
3. Alberto, G., Dorit, G., Aviva, T. Horowitz, D. T., Alexander, L. and Tali, S., Long-circulating liposomes for drug delivery in cancer therapy: a review of biodistribution studies in tumor bearing animals, Advanced Drug Delivery Reviews, 1997; 24: 337-344.
4. Laham, A. et al. Liposomally entrapped adenosine triphosphate: improved efficiency against experimental brain ischaemia in the rat, *Journal of Chromatography*, 1988; 440: 455-458.
5. Eldon E. Geisert, Nobel A. Del Mar, Jesse L. Owens, Eric G. Holmberg., Transfecting neurons and glia in the rat using pH-sensitive immunoliposomes, Neuroscience letters, 1995; 184: 40-43.
6. Shimon A., Doron F., Ayala Y., Wesley. R. Anderson, Danny O Helton, Thorsteinn L., Nicholas B., Emil P., Marcus E. Brewster, Formulation development for a Zidovudine chemical delivery system 2. Towards oral and non-parenteral dosage forms, *International Journal of Pharmaceutics*, 1995; 125: 31-43.
7. William M. Pardridge, Receptor mediated drug delivery to the brain, Advanced Drug Delivery Reviews, 1999; 36: 299-321.
8. Takashi Imaoka, Isao Date, Takashi Omato, Tatsuji Yasuda, Masaaki Tsuda, Invivo gene transfer into the adult mammalian central nervous system by continuous injection of plasmid DNA-cationic liposome complex, Brain Research, 1998; 780: 119-128.
9. William M. Pardridge, Brain drug targeting, Future of brain drug development, Cambridge University Press, 2001; 50-51.
10. R. H. Muller, C. Jacobs, O. Kayser, Nanosuspensions as particulate drug formulations in therapy. Rationale for development and what we can expect for the future, Advanced Drug Delivery Reviews, 2001; 47: 3-19.
11. Jorg Kreuter, Renad N. Alyautdin, Dimitri A. Kharkevich, Alexei A. Ivanov, Passage of peptide through the blood-brain barrier with colloidal polymer particles (nanoparticles), Brain Research, 1995; 674: 171-174.
12. R. Lobenberg, L. Araujo, J. Kreuter, Body distribution of azidothymidine bound to nanoparticles after oral administration, *European Journal of Pharmaceutics and Biopharmaceutics*, 1997; 44: 127-132.
13. Alessandro Bargoni, Roberta Cavalli, Gian Palao Zara, Anna Fundaro, Otto Caputo, Maria Rossa Gasco, Transmucosal transport of tobramycin incorporated in solid lipid nanoparticles (sin) after duodenal administration to rat part II- Tissue distribution, Pharmacological Research, 2001; 43: 497-502.
14. J. Kreuter, V. E. Petrov et al, Influence of the type of surfactant on the analgesic effects induced by the peptide dalargin after its delivery across the blood brain barrier using surfactant coated nanoparticles, *Journal of Controlled Release*, 1997; 49: 81-87.
15. Yechezkel Barenholz, Liposome application: problems and prospects, Current Opinion in Colloid & Interface Science, 2001; 6: 66-77.
16. Jorg Kreuter, Nanoparticulate systems for brain delivery of drugs, Advanced Drug Delivery Reviews, 2001; 47: 65-81.