Peptide Encapsulated Nanoparticles for Brain Drug Delivery

Abstract

The blood-brain barrier (BBB) is performing as a shielding barrier which is designed to protect the environment in the brain. It prevents the entry of dangerous substances into the brain but hinder the administration of some drugs to treat brain and central nervous system. Recently nanoparticles are playing a major role in targeted drug delivery. For the nanoparticles to act as effective carriers in targeting brain their surface must be decorated with specific ligands. Lately peptides have been recognized as potential ligands for encapsulating nanoparticles. It is proposed to synthesize the active part of Thioredoxin, a small redox protein in all organisms, on a PS-HDODA support. The selected sequence with a disulfide bridge and functional groups such as –SH and –NH2, is expected to stabilize the nanoparticles in drug delivery applications.

Keywords: BBB; Nanoparticles; Drug delivery; Peptides; Solid phase synthesis

Mini Review

Volume 3 Issue 5 - 2016

Jaya T Varkey*

Department of Chemistry, St.Teresa's College, India

***Corresponding author:** Jaya T Varkey, Department of Chemistry, St.Teresa's College, Ernakulam, Kochi, Kerala, 682035, India, Email: jayavarkey@yahoo.com

Received: October 29, 2016 | **Published:** December 05, 2016

Abbreviations: BBB: Blood Brain Barrier; NH2: Amidogen; CNS: Central Nervous System; pep-NPs: Peptide-Based Nanoparticles; PS: Polystyrene; HDODA: Hexanediol Diacrylate

Blood Brain Barrier (BBB)

BBB is acting as a highly selective membrane that separates the circulating blood from brain fluid [1]. This 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. Because of this, BBB prevents the treatment in a number of brain diseases by blocking the delivery of drugs [2] (Figure 1).

Nanoparticles in Drug Delivery

Nanopartilces have a size range of 1-100nm. These particles can be used to transport drug molecules across the BBB [3-5]. They can penetrate the barrier and deliver pharmaceuticals to brain for treatments against disorders like Parkinson's disease, Alzheimer's disease and brain tumors. It is very difficult to treat these disorders because there is not an efficient method available to transfer drugs across BBB. Many of the CNS active drugs could not pass through the BBB. Thus nanoparticles which can penetrate the BBB could be effectively used in drug delivery (Figure 2).

But nanoparticles tend to agglomerate to minimize their energy. Thus they try to react with their surroundings to attain some minimum energy for stabilization. In order to overcome this, Nanoparticles 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.

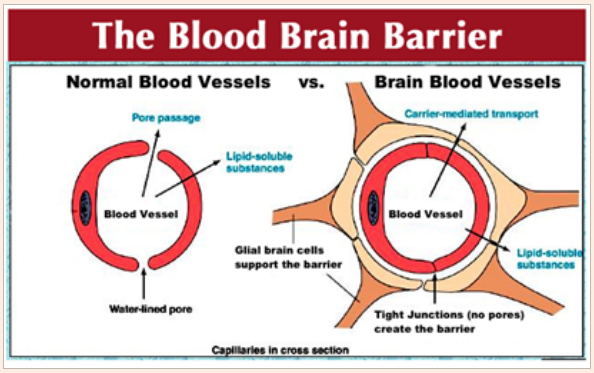


Figure 1: Blood brain barrier.

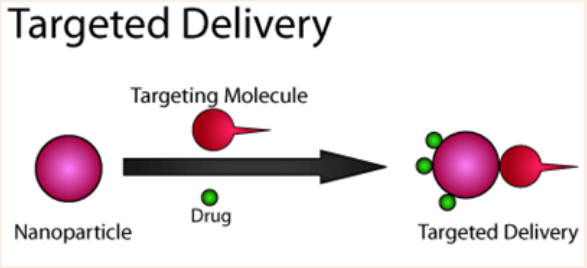


Figure 2: Targeted drug delivery using Nanoparticle.

Peptide Encapsulated Nanoparticles

Peptides are excellent biomolecular receptors and interactions

between peptide and nanoparticles have played a major role in controlled drug delivery [6]. Peptide-based nanoparticles (pep-NPs) are emerging as promising imaging and therapeutic agents against cancer due to their biocompatibility and tunability [7]. Recently peptides have been described as potential ligands for achieving the BBB targeting of nanocarriers. Peptides can be recognised by some receptors and transporters of brain endothelial cells allowing the endocytosis and in some cases the transcytosis of the nanoparticles decorated with them.

Peptides are selected to use for incorporation onto nanoparticles for imaging and drug delivery applications since they are found to be excellent candidates as biomolecular receptors and interactions between nanoparticle and peptides have played a significant role in controlled drug delivery. Coating gold nanoparticle surfaces with peptide molecule will expand the applications of these nanoparticles in biomedical sciences. It is proposed to synthesize peptide sequences which contain Cys and Lys residues and adsorb them on nanoparticle surface. Nanoparticles can cross the blood brain barrier and can be used in drug targeting and delivery systems. Functional groups such as -SH and –NH2 present a high affinity for gold, and since amino acids contain some of these groups, they are expected to stabilize gold nanoparticles [8].

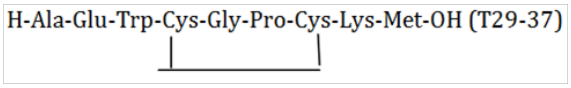
This method involves two approaches of detection and targeting. The detection approach involves the covalent coupling of cysteine in the selected sequences to a gold particle surface via sulphur-gold bond. This direct coupling affords a simple one-step procedure that produces particles with high surface coverage of peptide. The targeting approach involves electrospryaing of nanoparticles made from natural polymers that are biodegradable will be carried out, which will have the ability to target specific organs and tissues in the body. The qualitative and quantitative in vitro evaluation study of peptide conjugated nanoparticles to penetrate and cross a human brain endothelial cell model can be carried out.

Solid Phase Synthesis of Peptides

It is proposed to react a functional group (SH or -NH2) of a side chain of peptide molecules that are pre-formed via solid-phase peptide synthesis with gold particle surfaces. But one of the main difficulties in solid phase assembly of peptides is that of obtaining reasonable quantities of pure peptides. Isolation of proteins from natural resources can be laborious and often provides small quantities. Investigations dealing with the quantitative aspects of polymer-supported reactions have shown that the insoluble support does have a significant dynamic influence on the bound substrates. An efficient polymeric support for peptide synthesis should have optimum hydrophobic-hydrophilic balance compatible with the peptide being synthesized. It is proposed to utilize polystyrene (PS) cross-linked with 1, 6-hexanediol diacrylate (HDODA) as polymeric support [9]. The flexible nature and favorable swelling and solvation characteristics of PS-HDODA support has been demonstrated to be better than Merrifield resin [10].

Selection of Peptide Sequence

It is proposed to synthesize the following sequence which includes the active part of Thioredoxin [11],



Thioredoxin is a naturally occurring sulfur reducing protein containing 108 amino acids [12]. It is first identified in Escherichia coli. Since the activity of this enzyme is essential for cell growth and survival, it is a good target for anti-tumor therapy [13]. This enzyme is up-regulated in several types of cancer, including malignant mesothelioma [14]. Motexafin gadolinium is an inhibitor of thioredoxin reductase and ribonucleotide reductase. It has been proposed as a possible chemotherapeutic agent in the treatment of brain metastases.

Decorating Gold Nanoparticles with the Peptides

Gold particle bioconjugates are important constructs for cellular imaging [15]. Because of the large scattering cross section of metal particles, individual nanoparticles can be imaged under white-light illumination. This involves the covalent coupling of cysteine in the selected sequence to a particle surface via sulfur-gold bond [16]. This direct coupling affords a simple one-step procedure that produces particles with high surface coverage of peptide. One important aspect of thiol-gold chemistry is that the reaction proceeds at room temperature in aqueous solution.

Conclusion

Nanotechnology has opened a new path in drug delivery to brain and nanoparticles are developed as potential drug carriers. Nanocarriers are an emerging class of drug delivery systems that can easily deliver drugs to various compartments of the body. They possess unique features due to their size and they allow transport of a range of drugs. But because of their surface functionalization nanoparticle based drug delivery is complicated. Peptide conjugated nanoparticles are designed to explore their potential for brain targeting. The selected peptide sequences could be synthesized effectively on novel PS-HDODA support using solid phase methodology. Peptide-based nanoparticles (pep-NPs) are emerging as promising imaging and therapeutic agents against cancer due to their biocompatibility and tunability.

References

1. Butt AM, Jones HC, Abbott NJ (1990) Electrical resistance across the blood-brain barrier in anaesthetized rats: a developmental study. J Physiol 429: 47-62.

2. Garcia GE, Andrieux K, Gil S, Couvreur P (2005) Colloidal carriers and blood-brain barrier (BBB) translocation: A way to deliver drugs to the brain? Int J Pharm 298(2): 274-292.

3. Andrieux K, Couvreur P (2009) Polyalkylcyanoacrylate nanoparticles for delivery of drugs across the blood-brain barrier. Wiley Interdiscip Rev Nanomed Nanobiotechnol 1(15): 463-474.

4. Posadas I, Monteagudo S, Ceña V (2016) Nanoparticles for brain-specific drug and genetic material delivery, imaging and diagnosis. Nanomedicine 11(7): 833-849.

5. Ali IU, Chen X (2015) Penetrating the Blood-Brain Barrier: Promise of Novel Nanoplatforms and Delivery Vehicles. ACS Nano 9(10): 9470-9474.

6. Delehanty JB, Boeneman K, Bradburne CE, Robertson K, Bongard JE, et al. (2010) Peptides for specific intracellular delivery and targeting

of nanoparticles: implications for developing nanoparticle-mediated drug delivery. Ther Deliv 1(3): 411-433.

7. Xiao YF, Jie MM, Li BS, Hu CJ, Xie R, et al. (2015) Peptide-Based Treatment: A Promising Cancer Therapy. Journal of Immunology Research, p. 1-13.
8. Fan J, Chen S, Gao Y, (2003) Coating gold nanoparticles with peptide molecules via a peptide elongation approach. Colloids and Surfaces B: Biointerfaces 28(2-3): 199-207.
9. Varkey JT, Pillai VN (1998) Synthesis of thioredoxin partial sequences on 1, 6-hexanediol diacrylate (HDODA) - crosslinked polystyrene resin. J Pept Res 51(1): 49-54.
10. Varkey JT, Pillai VNR (1999) Merrifield resin and newly developed 1, 6-hexanediol diacrylate resin for solid phase peptide synthesis. A comparative study. Journal of applied polymer science 71: 1933-1939.
11. Holmgren A (1981) Thioredoxin: structure and functions. Trends in Biochemical Science 6: 26-29.
12. Holmgren A (1968) Thioredoxin - The Amino acid sequence of the protein from Escherichia coli B. Eur J Biochem 6(4): 475-484.
13. Mukherjee A, Martin SG (2008) The Thioredoxin system: a key target in tumour and endothelial cells. Br J Radiol 81: 557-568.
14. Kahlos K, Soini Y, Säily M, Koistinen P, Kakko S, et al. (2001) Up-regulation of thioredoxin and thioredoxin reductase in human malignant pleural mesothelioma. Int J Cancer 95(3): 198-204.
15. Smith L, Kuncic Z, Ostrikov K, Kumar S (2012) Nanoparticles in cancer imaging and therpy. Journal of Nanomaterials, p. 1-7.
16. Majzik A, Fülöp L, Csapó E, Bogár F, Martinek T, et al. (2010) Functionaliztion of gold nanoparticles with amino acids. B-amyloid peptide and fragment. Colloids Surf B Biointerfaces 81(1): 235-241.

Citation: Varkey JT (2016) Peptide Encapsulated Nanoparticles for Brain Drug Delivery. J Anal Pharm Res 3(5): 00069. DOI: 10.15406/japlr.2016.03.00069