Application of Nanotechnology for Targeted Brain Therapy

*Migbaru Keffale Bezabih and M. Balakrishnan*

1Department of Biomedical Science, College of Veterinary Medicine, Haramaya University, P.O. Box 301, Haramaya, Ethiopia
2Institute of Biotechnology, College of Natural Sciences, Addis Ababa University, P.O. Box 1176, Addis Ababa, Ethiopia

**Abstract:** The brain is a delicate organ that can be affected by several neurological disorders like that of other organs of the body but evolution built very efficient barriers to protect it from the invading pathogens and toxic chemicals. On the other hand, the presence of these barriers; a blood brain barrier and a blood-cerebrospinal fluid barrier control the free movement of solutes between blood and brain which hamper the effective delivery of therapeutics to the central nervous system. In consequence, many diseases of the central nervous system such as cancer, neurodegenerative diseases as well as neurological infections are remaining untreatable. In recent years, nanotechnology based effective drug delivery strategies such as manufacturing and use of liposomes, nanoparticles, vector peptides and amino acids have been started with the appropriate surface modification targeted to blood brain barrier and brain cerebrospinal fluid barriers. Even after application of this technology, successful delivery across the blood brain barrier has been achieved only for some therapeutic agents. This is due to narrow spectrum of developed few nanoparticles for specific agents. Therefore further researches should be done to wide up the range of the carrier particles.

**Key words:** Amino acids • Blood brain barrier • Liposomes • Nanoparticles • Peptides

**INTRODUCTION**

Neurological diseases are the fourth leading cause of death in the developed world after heart diseases, cancer and stroke. Approximately 24 million people worldwide suffer from neurological diseases such as neurodegeneration, malignant brain tumors and brain infection. Neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, Lewy body dementia and prion diseases are the leading neurological disorders. The start of these diseases can occur at any age but more common among the elderly people above 50 years of age. Neurological diseases treatment is difficult due to drug delivery limitations [1].

Drug delivery to the brain remains the major challenge for the treatment of all neurological diseases because of the numerous protective barriers surrounding the central nervous system, which restricts the entry of potential drugs into brain parenchyma [2]. These barriers are composed by blood brain barrier and blood-cerebrospinal fluid barrier, which are a highly specialized brain endothelial and epithelial structure of the fully differentiated neurovascular system. Three barrier layers regulate molecular exchange at the interfaces between blood and the neural tissue or its fluid spaces are the blood brain barrier formed by the cerebrovascular endothelial cells between blood and brain interstitial fluid, the blood-cerebrospinal fluid barrier formed by the choroid plexus epithelium between blood and ventricular cerebrospinal fluid and the third barrier is the arachnoids epithelium between blood and subarachnoid cerebrospinal fluid. Individual neurons are extremely close to the brain capillaries. Therefore, these barriers separate the neurons from components of the circulating blood and exert the greatest control over the immediate microenvironment of brain cells by selective transport mechanism [3].

Due to the presence of multiple endogenous transporters, blood brain barrier allows a selective entry of nutrients and minerals across it and limits the entry of...
foreign substances like drugs as well as neuropharmaceutical agents. This self-protection mechanism can hinder the penetration approximately 100% of large molecule drugs and greater than 98% of small molecule drugs into the central nervous system. The conventional drug delivery systems which release the drug into general circulation fail to deliver drugs effectively to the brain, which makes the central nervous system treatment ineffective. Therefore, the issue of central nervous system delivery of candidate drugs has been given more emphasis on developing and designing a better and effective approaches on with blood brain barrier drug targeting strategies [1].

Strategies for Central Nervous System Targeted Drug Delivery: There are several possible drug delivery strategies, such as direct surgical delivery, transient osmotic opening of the blood brain barrier, exploiting natural chemical transporters, high dose chemotherapy, or even biodegradable implants. But all of these methods have major limitations: they are invasive procedures, have toxic side effects and low efficiency and are not sufficiently safe. Therefore, the applications of nanotechnology have been launched [4].

A recent promising strategy for drug delivery to the brain is the application of nanotechnology, which is based on the development of small biomaterial components with the capacity of enveloping and distributing genetically engineered cells and the therapeutic drugs. This potential drug delivery technology is based on application of liposomes, nanoparticles, peptide vectors and transporter amino acids. Among these liposomes have received widespread attention as a carrier system for therapeutically active compounds, due to their unique characteristics such as capability to incorporate hydrophilic and hydrophobic drugs, good compatibility, low toxicity, lack of immune system activation and protect their cargo from degradation by plasma enzymes and transport their load to the targeted site of actions across biological membranes and the blood brain barrier in a better rate [5].

Ligand Conjugated Liposomes: Liposomes are spherical vesicle structures composed of a uni- or multilamellar lipid bilayer surrounding internal aqueous compartments and a relatively impermeable outer lipophilic phospholipid bilayer. Receptor-mediated endocytosis uses targeting ligands include peptides, proteins and antibodies that specifically bind to receptors expressed on the brain endothelial cells [6]. The most studied receptor used for drug targeting to the blood brain barrier is the transferrin receptor, which is highly expressed on endothelial cells of the blood–brain barrier. The natural ligand for this receptor is iron-bound transferrin (Holo-transferrin), which has a high affinity for the transferrin receptor. Endogenous large-molecule peptides such as transferrin, insulin and leptin cross the blood brain barrier through attachment to such receptors and cross through receptor-mediated endocytosis [7].

Lactoferrin-Conjugated Liposomes: One prospective modality for delivering drugs for brain diseases treatment and for transporting the nuclear imaging probe for neurodegenerative diseases diagnosis are through the receptor-mediated targeting on luminal side of the blood brain barrier. Lactoferrin is a single-chain iron-binding glycoprotein containing 690 amino acids folded into two globular lobes, which can penetrate the blood brain barrier through receptor-mediated transcytosis. Due to the less concentration of endogenous lactoferrin than transferrin, lactoferrin can be observed to exhibit better blood brain barrier uptake than transferrin resulting by the less competitive inhibition. As such, lactoferrin has been used to enhance the polymer-based drug delivery system and super paramagnetic iron oxide based magnetic resonance imaging contrast agent to brain [8]. Also the lactoferrin conjugated peptidoethylinglycolated liposome was constructed for the treatment of glioma as a novel brain delivery system [9].

Biodegradable Polymeric Nanoparticles: In recent years, gene therapy (Using genetically engineered cells) has evolved as a new treatment for brain diseases, especially for cancer and neurodegenerative diseases [10]. Biodegradable polymeric nanoparticles with appropriate surface modifications can deliver these therapeutic agents beyond the blood brain barrier for diagnostic and therapeutic applications in neurological disorders. The targeting agents have been incorporated into nanoparticulate carriers bearing ligands or antibodies for recognition by cell surface receptors expressed by target cells. Thus, ideal brain cancer therapeutic delivery nanoparticles contain the anti-cancer agent in the core of a polymeric sheet, whose surface has been decorated with a blood brain barrier targeting and transport-enhancing molecule and has enough positive charges to enhance uptake by brain tumor vasculature [11].
Encapsulated Polybutylcyanoacrylate Nanoparticles:
One strategy for delivering drugs across the blood brain barrier has been encasing the compounds within nanoparticles. For example, researchers have encapsulated chemotherapy agents and other drugs in 250-nm-diameter nanoparticles using polybutylcyanoacrylate. These small polybutylcyanoacrylate nanoparticles are coated with Tween-80 nanoparticles, which apparently bind apolipoprotein E to the particles. This coating of the small lipoprotein with apolipoprotein E seems to mask the nanoparticle and reduce the density of lipoprotein. These nanoparticles are endocytosed by the endothelium of the blood brain barrier, allowing entry of the particle into the endothelial cell. The drug can then diffuse or be effluxed into the brain parenchyma. Numerous compounds have been encapsulated this way, including doxorubicin which is an effective drug for cancer therapy [12].

Limitations of Nanotechnology Assisted Drug Delivery:
Despite all the wonderful advantages, applications of nanotechnology do have some limitations when compared with conventional methods of drug delivery such as nanoparticle encapsulated drugs require a high production cost; nanoparticles may have leakage and fusion of encapsulated drugs; their phospholipid layers may undergo oxidation and hydrolysis; the carriers have a shorter half-life and lower solubility [14].

CONCLUSION
The treatment of central nervous system diseases is particularly challenging because the delivery of therapeutic molecules to the brain is often precluded by a variety of physiological and biochemical obstacles that collectively comprise the blood brain barrier and blood cerebrospinal fluid barriers. These barriers are not only as a static anatomical barrier to free diffusion but also as a highly complex interface that react and interact with a range of blood-borne factors and signals produced within the central nervous system, which modulate its barrier function and activity. Many promising therapeutic molecules failed in their clinical trial because they cannot cross these barriers in sufficient quantity to be effective. In consequence the patients were suffering from many types of central nervous system diseases and remains with poor prognosis, but in recent year’s nanotechnology assisted drug delivery techniques have been developed, which provide reasonable hope to mitigate the exclusive effect of dreadful barriers shielding the central nervous system. Even substantial progresses have been seen on improvement against the effect of the barriers, vigorous research efforts should be done to develop more therapeutic and less toxic drugs and suitable carrier molecules to their central nervous system targets.

REFERENCES


