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Nanotechnology as a Targeted Drug Delivery System to Brain

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Abstract

Improvement of drugs acting on central nervous system (CNS) will be technology constrained. The drugs with large particles cannot be delivered to brain owing to lack of functional platform for drug targeting. Around 1.5 billion individuals worldwide are experiencing different kind of neurological disorders. To overcome this issue pharmaceutical innovation is advancing producing the nanoparticles. Legitimate utilization of nanomedicines (nanoparticles) is one of the approaches to control the CNS illness all over world. Nanoparticles are particles between 1 nm to 100 nm in size. Nanotechnology is conceivable to convey the drugs to the particular site of the tissue across the Blood-Brain Barrier (BBB). Various sorts of nanoparticle are accessible for treatment of CNS diseases. These are polymer based nanoparticles, solid lipid nanoparticles, lipid based nanoparticles and many more.

Keywords: ***Nanomedicines; Targeted drug delivery system; Blood-brain barrier; Neurological disorders.***

Introduction

For over a century, the CNS drug advancement is technology driven, focusing on conveying of large molecules drugs, for example, antimicrobial drugs, antisence medications, and recombinant proteins. However, because of lack of functional platform for central nervous system acting drugs focusing owing to the large size molecules medication cannot be transported to brain, and thus the complete therapeutics effect of such drugs cannot be achieved [1,2]. To meet this issue cutting edge pharmaceutical innovation producing the nanoparticles. Nanoparticles are particles between 1 nm to 100 nm in size. In nanotechnology; a molecule is characterized as a little transporter that carries on all in all unit concerning its vehicle and properties. Particles are further classified based on diameter [3,4]. The smallest size and great mobility properties give nanoparticles improve penetration through blood-brain barrier (BBB) as focusing on medication conveyance framework. Around 1.5 billion individuals worldwide are suffering from different sort of neurological conditions like meningitis, encephalitis, neurodegenerative illnesses, for example, Alzheimer, Parkinson's sickness and tumors, for example, glioblastoma multiforme [5-8].

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Therefore, effective and targeted treatment is in strong demand from patients. It is projected that the number of people with CNS illness will be approximately 1.9 billion by 2020, unless effective measures are undertaken [9]. Researchers have been developing novel technologies to overcome this problem. Nanotechnology gives the nanomedicine and it is additionally being better impact to enhance the CNS issue. Nanomedicine, the use of nanotechnology to medicinal services, holds incredible guarantee for advancing restorative medications, rapid diagnosis, imaging, drug transport, and tissue degeneration. Nanomaterials and nano-devices are now clinically approved, and different products are being assessed in clinical trials [10]. Nanoparticle systems in CNS targeted medication treatment give better penetration of diagnostic and therapeutic compounds, and a diminished danger in contrast with customary medicines. By utilizing nanotechnology, it is conceivable to transport the medication to the target tissue over the BBB, deliver the drug at a controlled rate, and avoids degradation processes. Lessening of toxicity to peripheral organs and biodegradability can likewise be accomplished with these systems. Numerous therapeutic compounds are poorly soluble or totally insoluble in aqueous solutions. These medications give difficulties to transport them orally or parentally, however these agents can have huge advantages when formulated through nanoparticle innovation. More effective utilization of the medication can be acknowledged both by disposing of liver metabolism system and directly focusing the brain [11]. Targeted drug delivery is a method for aggregating drugs at a particular site in relative to other parts of the body. This enhances efficacy and minimizes adverse symptoms. Drug targeting is the conveyance of medications to receptors or organs or some other particular desired part of the body to transport the medications only. In this review article we attempt to highlight how the nanoparticles work to cross blood-brain barrier as a targeting drug delivery system [12].

The Blood-Brain Barrier

The blood-brain barrier (BBB) is a selectively permeable barrier that isolates the flowing blood from the brain extracellular fluid. The BBB comprises of a monolayer of polarized endothelial cells (EC) associated by complex tight junctions (TJ). It is a consistent zipper-like tight junctioned endothelial cell layer. These tight junctions (TJ) are totally impeded and adherent junctions (200 Å) [13,14]. Owing to this reason, these tight endothelium junctions can be approximately 100 times tighter than other narrow endothelium junctions. The structure of these tight junctions was first determined in the 1960s. The increased electrical resistance at the TJ strains para-cellular movement of substances into the brain. Proteins of the adherent junction work as per TJ proteins for cellular adherence. Astrocytes (glial cells) in the extracellular matrix envelope the vessels and impact transport over the EC [15-18]. Questions once emerged in the role of astrocytes in BBB. It is currently acknowledged that there are 20 nm crevices between adjacent astrocytes. P-glycoproteins (P-gp) on apical EC layer efflux substances from brain into circulatory system (FIG. 1). Foot projections from astrocytes frame a perplexing system encompassing the vessels and this nearby cell affiliation is essential in induction and support of the hindrance properties. Axonal projections from neurons onto arteriolar smooth muscle contain vasoactive neurotransmitters and peptides and control local cerebral blood.

Blood-Brain Barrier (BBB) Physiology

The principle function of the blood-brain barrier is to secure the brain and keep it isolated from destructive toxins that are conceivably in the circulatory system. The blood-brain barrier permits the transport of water, some gasses, and lipid solvent molecules by passive diffusion [19,20].

The blood-brain barrier acts viably to shield the brain from numerous regular bacterial diseases. Along these lines, contaminations of the brain are exceptionally uncommon. However, since antibodies are too large to cross the blood-brain

barrier, diseases of the brain which do happen are severe and complex to treat. Viruses effectively cross the blood-brain barrier, notwithstanding, joining themselves to circulating immune cells. BBB expresses certain enzymes like peptidases along with several cytosolic enzymes and efflux p-glycoprotein system that aids effluxion of drugs from the endothelial cells back into the blood which helps in its further protecting action towards the brain microenvironment [22,23]. Thus the BBB is frequently the rate restricting component in deciding pervasion of restorative medications into the brain.

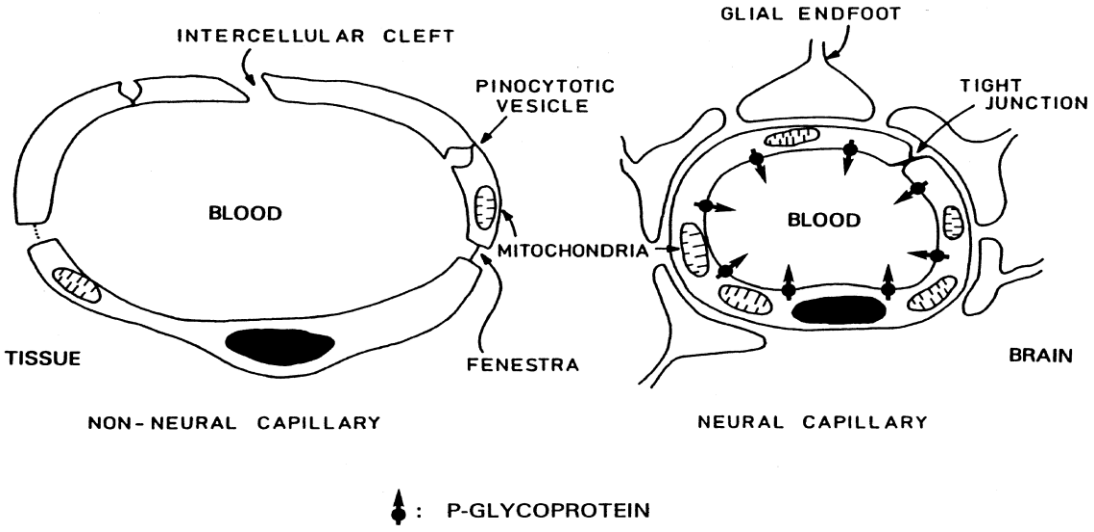

FIG. 1. **P-glycoprotein localization and activity in the blood-brain barrier [21].**

BBB function as a dynamic biological entity, in which active metabolism system and carrier-mediated transports. The transport of medications to CNS through the cardiovascular system is frequently blocked by considerable barriers viz. the BBB and the blood cerebrospinal fluid barrier (BCB) [24-27]. The BBB limits both transcellular and para-cellular passage of cells and molecules from the systemic circulation into the CNS and vice versa. Transcellular transport of hydrophilic particles is constrained because of a low rate of transcytotic vesicles, a to a great degree low pinocytotic action, articulation of dynamic efflux film pumps of the ATP-restricting cassette (ABC) family, for example, P-glycoprotein, and high metabolic action (cytosolic compounds and transporters) [28]. The tight junctions between endothelial cell results in a high trans endothelial electrical resistance of 1500 $\Omega.cm^2$ to 2000 $\Omega.cm^2$ contrasted with 3 $\Omega.cm^2$ to 33 $\Omega.cm^2$ of others tissues which decreases the fluid based para-cellular dispersion that is seen in another organ [29-31].

Nanoparticle Drug Targeting to the Brain

Neurological illnesses are an imperative reason for mortality and constitute 12% of aggregate deaths around the world [32]. Among the neurological conditions, Alzheimer and different dementias are assessed to constitute 2.84% of the aggregate deaths, while cerebral vascular illness constitute around 8% of the aggregate deaths in high income nations in 2005 [33].

In these above capacities it has been clear that nanoparticle is effectively focused to the brain if it effectively crosses the blood-brain barrier (BBB), and it will be lipid soluble, for the most part dynamic in passive diffusion [34-36]. It should be noted that NPs are articles measured around 1 nm and 100 nm that work all in all unit as far as transport and properties. In this way, nanotherapy is one of the imperative treatments to minimize the rate of mortality in CNS ailments in all over world [37,38].

Nanoparticle focused to the brain in taking after strides: Nanoparticle drug concentration expanding the inside, or at the luminal surface of BBB cells, building up a local high concentration gradient amongst blood and brain, higher than that realistic after systemic administration of the free medication The gradient ought to then support the improved passive diffusion of the medication [39-42]. With respect to illustration, this undertaking could be acknowledged by integrating NPs functionalized to target brain slender endothelial cells. This feature can be taken after or not by their consequent uptake from focused cells [43]. By entering into the CNS, nanoparticles carry the medication. This assignment can be acknowledged empowering NPs focusing of brain thin endothelial cells and their ensuing transcellular entry over the BBB [44-47].

Hindrances in Drug Targeting to the Brain

In this above bit of the article we plainly comprehended that little molecules promptly cross the BBB. In any case, actually, <2% of every little molecule crosses the BBB effortlessly. In the comprehensive restorative chemistry (CMC) database, there are >7000 drugs set up, and just 5% of these medications treat the CNS illnesses [48]. It has been researched that 100% of large molecule medications and 98% of small molecule drugs don't cross BBB. For a small molecule medication to cross the BBB in critical amounts, the molecule must have two imperative qualities like molecular mass must be under 400 Da and high lipid solvency [49-51]. Because of these reasons the brain drug focusing on turns out to be more troublesome for the pharmaceutical researchers. Presently it is an extremely difficult to all pharmaceutical organization around the world how the enhance brain targeting on medication delivery and minimize the CNS illness.

Types of Nanoparticles Targeting to Brain

Lipid based nanoparticles

Liposomes: Liposomes, initially depicted in 1965 are established medication and gene delivery carriers with clinical confirmation of adequacy and a few economically accessible endorsed clinical formulations [52,53]. Liposomes are little manufactured vesicles of spherical shape that can be made from cholesterol and natural nontoxic phospholipids. Because of their size and hydrophobic and hydrophilic character (other than biocompatibility), liposomes are promising frameworks for medication delivery Liposomes are the first generation of nanoparticulate medication delivery frameworks and are constituted by one or more vesicular bilayers (lamellae) made out of amphiphilic lipids, delimiting an inner fluid compartment. Liposomes have been to a great extent used for brain drug access, for the treatment of cerebral ischemia, for transport of opioid peptides and cerebrum tumors [54]. Liposomes can trap both hydrophobic and hydrophilic molecules, maintain a strategic distance from decay of the captured mixes, and release at the assigned targets. In view of their biocompatibility, biodegradability, low toxicity, and bent to trap both hydrophilic furthermore, lipophilic medications and disentangle site-particular medication conveyance to tumor tissues [55].

Cationic liposomes: Cationic liposomes containing positively charged lipids have been produced and at first utilized as transfection vehicles, to transport genetic material (DNA) into the cell, maintaining a strategic prevention from the lysosomal digestion. One case of cationic liposome utilizes bolaphiles, which contain hydrophilic groups encompassing a hydrophobic chain to reinforce the limit of the nano-vesicle containing the medication. Bolaphiles or bolaamphiphiles can cross the BBB, and they permit controlled discharge of the medication to target locales [56].

Solid lipid nanoparticles (SLNs): These are stable lipid based nanocarriers with a strong hydrophobic lipid center, in which the medication can be dispersed. They are made with biocompatible lipids for example, fatty acids, triglycerides, or waxes. They are by and large of small size permitting them to cross tight endothelial cells of the BBB and break from the

reticuloendothelial system (RES) [57,58]. High-pressure homogenization or micro-emulsification can be utilized for formulation of nanoparticles. Moreover, functionalizing the surface of solid lipid nanoparticles with polyethylene glycol (PEG) can bring about expanded BBB porosity. The upsides of SLNs are controlled release of the incorporated medication can be accomplished up to a few weeks. There is additionally a degree for medication targeting by coating or connecting with the legends. In their small molecule size, they can cross the liver and spleen effortlessly [59].

Polymer-based nanoparticles

Polymeric nanoparticles: In the course of the most recent decade polymeric nanoparticles have grabbed attention of scientists in targeting drug molecules to brain. Polymeric nanoparticles are nanosized transporters (1 nm to 1000 nm), made of natural or synthetic polymers, in which the medication can be stacked in the solid state or in solution, or adsorbed or chemically connected to the surface [60]. Presently, the utilization of polymeric nanoparticle is a standout amongst the most encouraging approaches for CNS drug conveyance. As the name proposes, polymeric nanoparticles are nanoparticles which are made from polymers. Most popular ones are polylactides (PLA), polyglycolides (PGA), Poly (lactide-co-glycolides) (PLGA), polyanhydrides, polycyanoacrylates, and polycaprolactone. Disregarding improvement of different manufactured and semi-engineered polymers, additionally regular polymers, for example, chitosan can be used. Nanoparticles can be synthesized from preformed polymers or from a monomer amid its polymerization, as on account of alkyl cyanoacrylates [61].

Nanospheres or nanocapsules can be orchestrated, with their resultant structures that are subordinate upon the innovation utilized in the assembling. Nanospheres are the thick polymeric frameworks in which medication are dispersed, whereas nanocapsules present a fluid center encompassed by a polymeric shell. Most procedures including the polymerization of monomers incorporate the expansion of the monomer into the dispersed phase of an emulsion, a converse microemulsion or broke down into a non-dissolvable of the polymer [62]. At long last, two principle approaches have been proposed for the arrangement of nanoparticles by manufactured polymers. The hypothesis of the principal plan takes after the emulsification of a water-immiscible organic solution of the polymer, in a surfactant-containing watery phase, and took after by solvent evaporation. The second approach takes after the precipitation of a polymer after the expansion of a non-solvent of the polymer [63].

Chen et al. [33] have stated that polymeric nanoparticles as appropriate delivery systems for brain. They have plot different systems for nanoparticle interceded drug uptake by the brain [64]. These include:

- Upgraded maintenance in the brain-blood vessels, with an adsorption on to the capillary walls, bringing about a high concentration gradient across the BBB.
- Opening of tight junctions because of the presence of nanoparticles.
- Transcytosis of nanoparticles through the endothelium.

Points of interest of polymeric nanoparticles are increase in the stability of any volatile pharmaceutical agents effortlessly and efficiently manufactured in large amounts by a huge number of strategies, delivering a higher concentration of pharmaceutical compound to a target site.

Polymeric micelles: Polymeric micelles are nano measured water dispersible groups of polymeric particles and thus are brilliant nanocarriers for PDT (photodynamic treatment) drugs. Along with photosensitizing agents, iron oxide nanoparticles were encapsulated inside the nanocarrier, which permitted them to respond to externally applied magnetic field. This

magnetically guided drug delivery would allow for the use of lower concentration of drug to deliver a therapeutic dose, significantly reducing the amount of PDT drugs that accumulate in normal tissue. Photodynamic therapy (PDT) is a novel therapy technique, used for treating the superficial tumors. In this therapy, photosensitizing agents are used for photochemical irradiation of malignant cells. Stability can be improved by cross linking between the shell and the core chains. Additional tenable features of polymeric micelles are the possibility to render them responsive to external stimuli (pH, light, temperature, ultrasound, etc.) [65].

Dendrimers: Dendrimers are stretched polymers, helping the structure of a tree. A dendrimer regularly symmetric around the center, and when adequately broadened it regularly embraces a spheroidal three-dimensional morphology in water. Dendrimers display a profoundly expanded, 3D engineering and contain an initiator center, a few inside layers made out of rehashing units, and various dynamic surface terminal gatherings [66-68]. The branches and surface gatherings of dendrimers increment exponentially in number with the generation (G) of the dendrimers, while the distance across of dendrimers increments by around 1 nm with the generation.

A few points of interest of dendrimers incorporate their spreading structure and the control of surface usefulness, making them phenomenal bearers for more than one single medication to the brain; they have a high stacking limit and low toxicity. Impediments of their utilization incorporate the high cost of assembling and the requirement for evaluation of the long term human wellbeing outcomes of dendrimer introduction *in vivo* [67-72].

Conclusion

In this above discussion it is presumed that nanotechnology formed to transport drugs into brain through BBB for patients with brain tumor and different CNS illness treatment. Currently there are many medications which are utilized as a nanomedicine, their course of organization and use of utilization. NPs offer clinical points of interest for medication conveyance, for example, diminished medication measurement, minimized reactions, greater medication half-life, and the likelihood to improve drug crossing over the BBB. In this way, the point of nanomedical science is to diminish the CNS illness all over world.

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