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Tumor targeting and brain specific delivery and strategies: A review

Manish Kumar*, Arpita Singh, Amresh Gupta

Goel Institute of Pharmacy and Sciences, Faizabad Road, Lucknow (UP) India-226028

ABSTRACT

Brain tumors represent one of the most challenging and difficult areas in unmet medical needs. Tumor-targeted and brain drug delivery systems, increase drug accumulation in the tumor region, and also reduce toxicity in normal brain and peripheral tissue, are a promising new approach to brain tumor treatments. When brain-tumors exhibit numerous notable characteristics relative to tumors growing in peripheral tissues, potential targets based on continuously changing vascular characteristics and the microenvironment can be utilized to facilitate effective brain tumor-targeted drug delivery. In present review, we briery describe the physiological characteristics of brain tumors, including blood–brain/brain tumor barriers, the tumor microenvironment, and tumor stem cells. We are also discussing in review targeted delivery strategies and introduce a systematic targeted drug delivery strategy to overcome the challenges. A disturbing fact about the delivery of drugs to the CNS in the presence of a blood-brain barrier that has a tendency to impair the drug distribution and denotes the general barrier for the development of CNS drugs. Neuro-peptides and many more drugs which are hydrophilic in nature possibly will encompass the intricacy while passing the blood-brain barrier. The net amount of delivered drugs and their capability to gain access to the pertinent target sites are the main considering points for CNS drug development. In this review, we will discuss about methodologies for targeting site of brain.

Keyword : brain barrier, drug delivery to brain, tumor microenvironment

INTRODUCTION

In the central nervous system, targeted action can be achieved by direct administration of the drugs in to the CNS[1]. Blood brain barrier can considerably impair the effect of the large number of drugs (e.g., antibiotics, antineoplastic agents and Neuropeptides-CNS stimulant drug)because of its obstinate hindrance affect[2]. From some recent studies, it has been represented that the blood brain barrier is usually does not cross by almost 100% of large molecule drugs and 98% of small molecule drugs[3]. Currently, numerous approaches with enhanced pharmacodynamics effects, have been developed for the treatment of brain disorders[4]. Delivery of drug and discovery technologies are the two different but most important fields where advancement is required for drug delivery to the

brain[5]. Nanoparticles drug delivery system (NDDS) is one of the advanced technologies that can be utilized to deliver drug molecules directly into the brain and proved to be very effective against several CNS disorders. Even, the failure is also explained to the side effects of radiotherapy and poor outcome of usual chemotherapy. For several years, researchers have tried to deliver therapeutic agents to the tumor region effectively and reduce unnecessary drug accumulation in normal brain and peripheral tissues. In order to brain tumors, active targeted drug delivery systems have attracted extensive attention indecent decades. Because brain tumors get many notable characteristics from peripheral tumors due to their complicated oncogenesis, many factors must be taken into consideration for effective brain tumor-targeted drug delivery, such as the barriers included in the whole process, the tumor microenvironment, and tumor cells. Now different targets have been exploited to achieve the targeting therapy using nanocarriers[6].

NANOPARTICLES AS A TARGETING DRUG DELIVERY SYSTEM

Nanoparticle, ultrafine unit with dimensions measured in nanometers (nm; 1 nm = 10^{-9} meter). Because of their submicroscopic size, they have unique material characteristics, and manufactured nanoparticles may find practical applications in a variety of areas, including medicine, engineering, catalysis, and environmental remediation. In general, nanoparticle-based technologies center on opportunities for improving the efficiency, sustainability, and speed of already-existing processes. It possible because, relative to the materials used traditionally for industrial processes, nanoparticle-based technologies use less material, a large proportion of which is already in a more "reactive" state. Many type opportunities for nanoparticle-based technologies include the use of nanoscale zero-valent iron particles as a field-deployable means of remediating organ chlorine compounds, such as polychlorinated biphenyls (PCBs), in the environment. Nano zero-valent iron particles are able to permeate into rock layers in the ground and thus can neutralize the reactivity of organochlorines in deep aquifers. Another application of nanoparticles is those that stem from manipulating or arranging matter at the nanoscale to provide better coatings, composites, or additives and those that exploit the particles' quantum effects (e.g., quantum dots for imaging, nanowires for molecular electronics, and technologies for spintronics and molecular magnets).

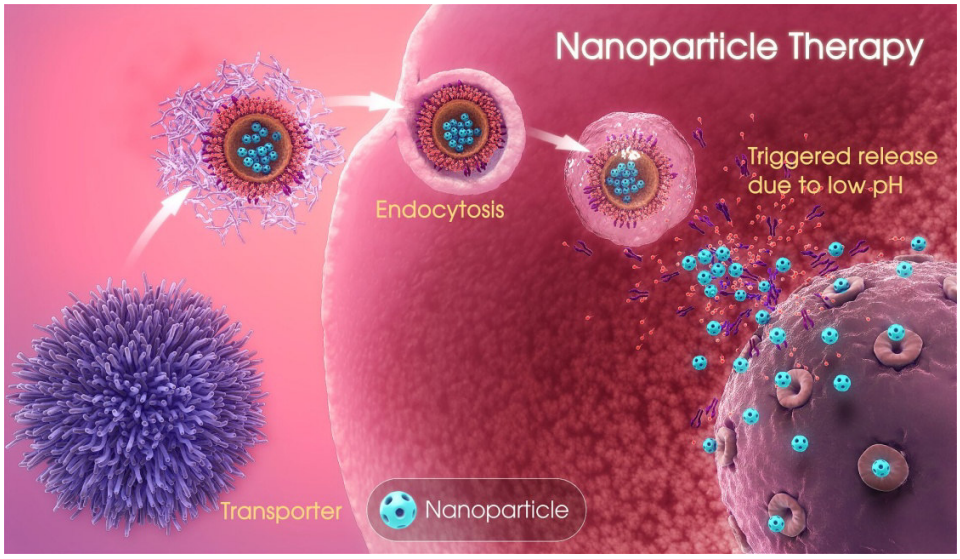

Fig – 1 – Nanoparticle therapy

TYPES OF NANOPARTICLES7

Depending on the arrangement of drug and polymer matrix, Nanoparticles are of two types:

1. Nanospheres

Spherical particles havingnanometric dimensions and acting as a drug carrier in which drug is enclosed inside the polymer matrix[8].

2. Nano capsules

Inner liquid core containing drug, and outer surface of nano particles are surrounded by the polymeric membrane [9]

BRAIN TARGETED DRUG DELIVERY RATE-LIMITING ROLE OF THE BBB IN BRAIN DRUG DEVELOPMENT

1. Blood brain barrier is the major confront toward brain targeted drug delivery[10].
2. BBB have efficient ability to restrict and separate the human brain from circulatory network, and only allow the transportation of molecules that play vital role in functional activity ofbrain[11].
3. It also limits the transport of water and lipid soluble substances from blood circulation into CNS[12].
4. Advancement in the perception of the cell biology of blood brain barrier has started the innovative path or opportunities for better drug delivery to the brain[13].
5. Various receptors, enzymes and transport systems have been recognized in the endothelium of BBB that restrain the molecules infiltration, for example protein and peptides are transported by Receptor-mediated transcytosis[14]

TRANSFER MECHANISM ACROSS BLOOD BRAIN BARRIER

In Blood Brain Barrier, several transport systems are present to control the transfer(either influx or efflux) of different essential solutes and drug molecules such as Diffusion(Passive and active diffusion), Facilitated diffusion, Active transport and Transcytosis[15].

BRAIN TARGETING TECHNOLOGIES

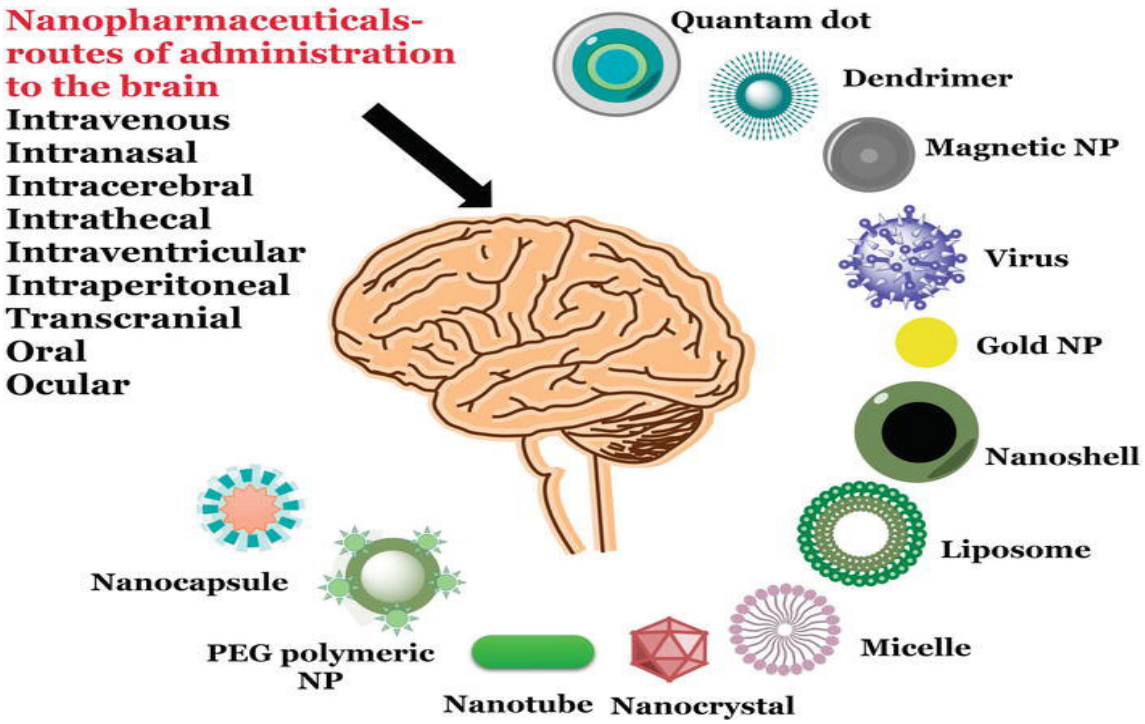

Fig – 2 – Nonpharmaceutical: A Boon to Brain-targeted Drug delivery

1. Noninvasive approach: Lapidate the drug molecules e.g., transnasal route[16].
2. Drug conjugates with liposomes and Nanoparticles[17].
3. Intrathecal and intracerebroventricular delivery of drug molecules into CNS by using different devices and needles[18].
4. Sustained and controlled release of drugs is considered along with systemic therapy in order to optimize the drug action into the CNS.

POSSIBLE SYSTEMS FOR DRUG DELIVERY TO THE BRAIN

1. Colloidal drug carriers' systems for example vesicle, macular solutions, liquid crystal dispersions, and liquid crystal dispersions (particle size range 10 to 400 nm) [19].
2. Nanotechnology[20].

NANOTECHNOLOGY

Improved drug delivery to the brain can be achieved by Nanotechnology, a more competent technology[21]. Materials used to prepare nanoparticles are Polyacetates, poly (alkyl cyanoacrylates), polysaccharides Copolymers, polysorbate-coated nanoparticles, etc.[22]

Mechanisms of Nanoparticle Transport across the blood-brain barrier.

There are six enhancing mechanisms for the transport of nanoparticles across the blood-brain barrier

1. Adhesion of nanoparticles to brain blood vessel walls[23]
2. Fluidization of BBB endothelium by surfactants[24]
3. Opening of tight junctions of the endothelium[25]
4. Transcytosis across the brain endothelial cells[26]
5. Blockage of the glycoprotein in the brain endothelial cells [27]
6. Endocytosis by the brain vascular endothelial cells[28]

NANOPARTICULATE SYSTEMS FOR BRAIN TARGETED DELIVERY OF DRUGS

The size range of Nanoparticles is about 10 and 1000 nm and are usually made of various polymers (natural/artificial) [29]. Nanoparticles have the ability to entrap and encapsulate the drug molecules[30]. Examples of Nanoparticles drugs are vaccines and anticancer drugs to treat metastatic brain tumors [31]. At the same time the, employing of nanoparticles in the field of ophthalmic and oral delivery was also investigated[32].

FUTURE ASPECTS OF THE BRAIN TARGETING TECHNOLOGICAL CHALLENGES THAT NEED TO BE ADDRESSED ARE

1. Attainment of controlled release profiles particularly for sensitive drugs[33]. Improvement/enhancement of nanoparticles release from implantable devices/nanochips [34].
2. cytotoxicity of nanoparticles should be reduced to improve biocompatibility[35].
3. Multifunctional nanoparticles[36].
4. Universal formulation schemes that can be used as I/V, I/M, or oral drugs.
5. Nanoparticles for tissue engineering such as cytokines to restrain cellular growth, discrimination and promote regeneration[37].
6. Encapsulation of implants by nanoparticles containing biodegradable polymer for sustained release[38],[39].

BARRIERS TO TARGETED DRUG DELIVERY STRATEGIES

The oncogenesis of gliomas is complicated, with various barriers preventing the drug from reaching the tumor sites. There are three main barriers for brain tumor treatment: the blood–brain barrier (BBB), the blood–brain tumor barrier (BBTB), and a relatively weak EPR effect. Specific brain tumor development stages require corresponding barrier targeting treatment strategies.

BBB targeting strategies and related drug delivery systems. At the early stage of brain tumor

development and at the infiltration growth region of the tumor, the blood–brain barrier remains intact. The blood–brain barrier, which acts as a natural guard to protect the brain from harmful substances in the bloodstream while supplying the brain with the necessary nutrients for proper function, is the key challenge for delivering drugs to brain tumor[40]. The BBB is a specialized system of capillary endothelial cells which are partially covered by pericytes and basement membrane, and almost fully surrounded by the end feet of astrocytes, preventing approximately 98% of the small molecules and nearly 100% of large molecules including recombinant proteins and genes from being transported into the brain and reaching the tumor sites[41,42]. The BBB strictly limits drug transport into the brain by serving as a physical (tight junctions), metabolic (enzymes) and immunological barrier. To tackle this challenge, many kinds of active targeting strategies were adopted for developing effective drug delivery systems to the brain. The active targeting systems are mainly divided into absorptive-mediated transcytosis (AMT), transporter-mediated transcytosis, and receptor-mediated endocytosis (RMT) [43].

CONCLUSION

Now a day, many young researchers are attracted to brain targeting due to its immense application in the treatment of various CNS diseases because most drugs are unable to cross the Blood-brain barrier. This short review discusses one of the novel technology "Nanotechnologies" that has been developed to target the brain and possess various clinical benefits such as reduced drug dose, fewer side effects, non-invasive routes, and better patient compliance. One common dual-targeting drug delivery system was the combination of trans-BBB targeting and brain tumor cell targeting in two ways. The first was dual-targeting moiety modification such as transferring and wheat germ agglutinin (WGA), and p-amino phenyl-α-d-aminopyrine side (MAN) and transferring the second one is a single-targeting moiety that targets both BBB and tumor cells, such as angiopep-2 targeting to LRP over expressed on both BBB and glioma cells. Another dual-targeting drug delivery system was combining trans-BBTB targeting with brain tumor cell targeting.

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