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Roles of Nanomedicine in Clinical Neuroscience

Alain L Fymat*

International Institute of Medicine and Science, USA

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***Corresponding author:** Alain L Fymat, International Institute of Medicine and Science, USA, Tel: 760-507-6862; Email: alain.fymat@fiimas.org

Abbreviations: NPs: Nanoparticles; BBB: Blood Brain Barrier; GBMs: Glioblastomas; H3M: 3-Helix Micelles; PD: Parkinson's Disease;

Introduction

One of the most promising applications of nanomedicine principles is in clinical neuroscience, particularly in the treatment of glioblastomas and neurological disorders (epilepsy, Parkinson's disease; Alzheimer's disease, etc.). Here, specially-designed nanoparticles (NPs) delivered by specially-designed nanocarriers are able to cross the blood brain barrier (BBB) to deliver their payload at pre-defined location(s) according to specified time- and dose-fractionations while remaining unnoticed by the immune system. Several NPs are utilized, including: nutshells (that can be targeted to bond to cancerous cells by conjugated antibodies or peptides to anopheles' surfaces); platelet-coated NPs (that can deliver higher doses of medication drugs to targeted sites, thus greatly enhancing their therapeutic effects); biocompatible and biodegradable gelatin NPs (that can deliver multiple drugs); and shape-shifting engineered NPs (that can be tailored to deliver drugs to specified tumors and nowhere else).

The NPs employed consist of three layers: a core vesicle with a double-layered membrane that is filled with water and hydrophilic and/or hydrophobic drugs; a multi-layered shell; and an exterior shell for targeting the NPs to the pathologies under treatment while preventing them from being detected by the immune system. The purpose of a multi-layered shell is multi-pronged: stabilize the NPs; prevent drug leakage; allow passage through the BBB; target the NPs to the slightly acidic environment of brain tumors (glioblastomas); minimize the interactions of the NPs with non-cancerous cells; and pass unnoticed by the immune system. The multi-layered NPs can also transport drugs that are not easily stored in the core (e.g., highly charged nucleic acids). These molecules can be separated from drugs in the core that could otherwise inactivate their therapeutic effects (e.g., plasma drugs).

The underlying process used to deliver the drugs involves at least three steps: encapsulation of the drugs; successful delivery of the said drugs to the targeted area; and successful release of those drugs there. To this end, several nanocarriers have been developed. These carriers usually encapsulate drugs through long-range electrostatic interactions wherein the carrier attracts oppositely-charged medicines. Other tools are available to trigger the release of the drugs, e.g. magnetic fields, different ph-values, etc., but, in each case, the problem of efficiency of the drug release remains. Work is still needed to determine the most effective nanotechnologies for brain pathologies and tumors. Nonetheless, challenges still remain, including how not to let the medicine(s) act before they reach the right address.

There are several clinical advantages to the NPs thus delivered. Specifically, they: circulate throughout the bloodstream without being attacked by the immune system; preferentially bind to cancerous areas allowing them to deliver and release their drug payloads specifically there; are non-toxic as the platelet membranes are nanoparticle cores made of a biodegradable polymer that can be safely metabolized by the body; and can be packed with many small drug molecules that diffuse out of the polymer core and through the platelet membrane onto their targets.

Regarding the non-surgical treatment of glioblastomas (GBMs), the several FDA-approved drugs have had little impact so far because the BBB limits their accumulation. Utilizing nanotechnology principles, available drugs are made to cross the BBB in special liposomes (size~110nm). One potential such approach is represented by 3-helix micelles (H3M), a new family of nanocarriers consisting of a spherical assembly of ampiphilic, hydrophilic and lipophilic peptides and polymers. Micelles are

elongated self-assemblies of peptides and polymers; these are sub (light) microscopic particles (~20nm) of supramolecular character and crystalline structure that are detectable by hydrogels. More recently, they have been defined as one of two classes of colloidal particles, consisting of many molecules, the other class being single macromolecules of submicroscopic size. A micelle is thus a structural unit of the disperse phase in a gel, a unit whose repetition in three dimensions constitutes the micellar structure of the gel; it does not denote the individual particles in free suspension or solution, or the unit structure of a crystal. It can be detected by hydrogels of supramolecular character and crystalline structure. One principal advantage of H3Ms is they can cross the BBB and accumulate inside GBM tumors at nearly twice the concentration rate of current FDA-approved nanocarriers. Meet all the size and stability requirements for effectively delivering drugs to GBM tumors. They have shown good attributes, including long circulation, deep tumor penetration, and low accumulation in off-target organs (such as the liver and spleen). They open the possibility of treating GBMs via intravenous drug administration rather than employing invasive measures. While they have been demonstrated in rats using radiolabeling with copper (Cu-64) in combination with MRI and PET, their applications to humans remain pending.

Regarding neurological diseases, the BBB is demonstrably intimately interconnected with their cause, effect and treatment. It limits access to the brain of small nonpolar molecules by passive diffusion or catalyzed transport of large and/or polar molecules. Further, it hinders the delivery of most pharmaceuticals (diagnostic, therapeutic agents) to the brain. Still further, ABC efflux transporters at the BBB influence the brain uptake of a variety of therapeutic agents. For epilepsy, links have been proposed with the BBB condition. Additionally, a compromised BBB has been associated with seizures in a number of disorders. Not only congenital defects, such as GLUT1 deficiency, but acquired deficiencies, like those resulting from brain tumors, head trauma, etc., often result in seizure disorders. More recently systemic and immune triggers have been implicated in a leaky BBB and to neuroinflammation. Understanding the nature of the role of BBB in these disorders is imperative in the treatment of the disease, but the fundamental question of whether the compromised integrity of the BBB is a component of the etiology of epilepsy or a consequence of seizures remains unanswered. Additionally, drug resistance which affects ~ 30% of epileptic patient's remains an important focus of epilepsy research.

In the case of Parkinson's disease (PD), three important conclusions have already been reached. The standard drug, Dopamine, does not cross the BBB so it cannot be taken as a medicine to boost the brain's depleted levels of dopamine. However its precursor, Levodopa, can pass through the barrier to the brain where it is readily converted to Dopamine. Administration of this drug temporarily diminishes the motor symptoms of PD. Unfortunately, only~5–10% of the drug crosses the barrier with much of the remainder being metabolized to Dopamine elsewhere in the body, where it causes a variety of side effects. Next, the immunotherapeutic strategy for PD therapy relies on the assumption that alpha-synuclein is accessible in the extracellular space (trans-synaptic spreading), antibodies against alpha-synuclein reach the brain in sufficient quantity, and they trap alpha-synuclein aggregates when these are released ("spread") into the extracellular synaptic space. However, one important limitation of active and passive immunotherapy is that the low amount of antibodies passing the BBB may be overcome by coupling antibodies to the peptide penetration, as has recently been reported in a mouse PD model. Lastly, modulating the aggregation of alpha-synuclein aims to block or reduce the aggregation of its monomers to oligomers or later on to fibrils. Three drugs are close to or under very early development (ANLE138b, NPT200-11, and NPT100-18a). The advantage of these small molecules is that, in variance to antibodies employed in immunotherapeutic attempts, they readily pass the BBB. Thus, being able to traverse (or bypass) the BBB while delivering therapeutic compounds at the right locations, in the right dosage amounts, would herald a new approach to the treatment of PD. This is what nanomedicine and nanotechnology promise to do. However, while the technology is now well known, its application to PD has not yet been undertaken.

As seen, permeability of the BBB is one of the factors determining the bioavailability of therapeutic drugs and resistance to chemically different anti-Parkinson drugs. Unfortunately, there is no known theory of drug resistance in PD. BBB disruption after acute head trauma is a well-known pathologic finding in humans and also animals. This disruption may persist for weeks to years after the injury and may be associated with abnormal EEG activity. Whether this abnormal activity develops into PD is currently unknown, but observations have suggested that BBB disruption in conjunction with a slowing in EEG activity may be a precursor to seizures or tremors. Others have observed persistent BBB disruption in the absence of any evidence of active seizure/tremor foci. It has been demonstrated that with relatively severe loss of BBB function there is extravasations of serum albumin into capillary endothelial cells, basal lamina and neutropils. Thus, the BBB integrity is closely correlated to the electrophysiological properties of the tissue as evaluated by intra-operative EEG. More recently, systemic and immune triggers have been implicated in a leaky BBB and neuroinflammation. Understanding the nature of the role of BBB in PD and other neurological disorders is imperative from a treatment point of view. Nonetheless, the fundamental question of whether the compromised integrity of the BBB is a component of the etiology of PD or a consequence of it has remained unanswered so far.

In summary, nanotechnology will reduce the need for invasive surgery even though some devices (implanted catheters and reservoirs) will likely still be needed. Nanomaterials are

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improving the safety/efficacy of nanodevices. Nano-engineered probes can deliver drugs at the cellular level using nanofluidic channels. Microchips and biodegradable polymeric NP carriers may be more effective therapeutically for brain tumors. The next-generations: H3M micelles, nanoparticle nasal sprays and "sticky" NPs will further these advances and benefits. In the NP nasal spray, gold NPs of controlled size shape (spherical) and surface charge contain various medicines. The movement of NPs can be tracked by fluorescent tagging. The first experiments using locusts showed that, passing through the BBB, the NPs reached the brain and suffused in a matter of minutes. However, as of this writing, there is as yet no approved nanotechnology-based CNS drug. Nonetheless, while the safety of NPs must be satisfactorily resolved before human use, the future of nanobiotechnology in brain treatment is promising! With the constant refinement of existing nanotechnologies and the development of new ones, our ability to image, manipulate and explore the BBB will only improve, thereby enabling the next generation of therapeutic advances [1-25].

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