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Role of magnetic nanoparticles in targeted drug delivery for central nervous system

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ABSTRACT

Introduction: The treatment of neurological disease, such as brain cancer or neurodegenerative diseases, is one of the most difficult challenges in medicine. The major limitation in this therapy is caused by asthenia of some drugs injected to the blood vessel to reach the main tissue of brain. There are three substrate obstacles that adjust molecular exchange in junction between blood and neurotic tissue or its steep spaces: the brain endothelium which makes blood-brain barrier (BBB), the arachnoids epithelium which makes intermediate substrate of meninges and the choroid plexus epithelium, which secretes cerebrospinal fluid (CSF).

Methods: In recent years, some significant researches showed that magnetic nanoparticles (through conjugation of iron oxide NPs with hydrophilic polymer coatings of dextran) can be administered for impressive systemic and territorial transfer of therapeutics to the CNS. Nanoparticles also have the potential to revolutionize conventional imaging techniques. Conventional epitomize condition lack the association of high delicacy and high spatial precision required for molecular imaging.

Results: Magnetic Resonance Imaging (MRI) has high resolution, but lacks sensitivity to molecular signals, while high sensitivity nuclear medicine modalities such as Individual photon ejaculation calculated tomography and position emission tomography (PET) provide superb sensitivity, at the cost of reduced spatial resolution. Using nanoparticles in some conditions such as MRI can amazingly enhance delicacy, presenting the potential for high resolution molecular imaging. MRI has high spatial resolution, is non-invasive in nature and offers multiplanar tomographic capabilities. Nanoparticles can be managed to have magnetized specifications that can be acquired by MRI at low condensations and at the same time include lingads which target specific molecules. Iron oxide nanoparticles have been widely researched for MRI, as there are several types, namely magnetite (Fe_3O_4) and hematite (α-Fe_2O_3), among which magnetite is very promising, because of its proven biocompatibility. For molecular imaging purposes, superparamagnetic iron oxide nanoparticles (SPIONs) need to bind to a range of drugs, proteins, enzymes, antibodies, or other molecular targets. In conclusion, using magnetized nanoparticles as a drug delivering system is still determined by its biocompatibility and optional aiming to the favorable cell or tissue under the guidance of external magnetic field (MRI scanner).

Conclusion: Advances in current technologies and the expansion of magnetized nanoparticles as medicine transfer device to transfer medicine to tumor hypoxic zones have fast tracked in the past decade and led to the development of various magnetic nanoformulations such as liposomes, metallic, and polymeric nanoparticles. This technology will not only minimize invasive methods, nut also decrease side effects to intact fiber which are two primary concerns in conventional cancer therapies. The field of magnetic drug delivery is still at infancy, and combination of better magnetized medicine transfer device and association of multifunctional ligands are being continuously investigated so as to carry it from the bench-top to the clinic. Until Then the worries about the omission and long term toxicity remain barriers to clinical entry.

KEY WORDS: MRI, magnetic nanoparticles, magnetic drug delivery, CNS.

1. INTRODUCTION

Due to the instant need for ameliorate biomarkers and treatment for psychiatric, developmental, ulcerous, inflammatory, infectious and degenerative central nervous system (CNS) disorders, interest in nanoneuromedicine has increased amazingly, inflammatory, infectious and degenerative central nervous system (CNS) disorders (Rahmani Tanha, 2016; Fatehi, 2016; Gendelman, 2014). These, in whole or in part are a considerable societal responsibility due to increase in numbers of affected people and in illness intensity. Lost efficiency of a patient and his or her caregiver, and the fiscal and emotional responsibility cannot be overestimated. Necessity of better health care, therapy and diagnostics is essential. One of the ways to get this target is called nanotechnology. Indeed, new progresses of health care enables nanotechnologies and nanomedicine scope from biomarker detection containing neuroimaging to therapeutic applications for corruptive, degenerative and zymotic disturbance of the CNS (Fatehi,

2016; Jahangiri, 2016). This publication centralize on the running and subsequent potential of the field to positively modify clinical results many CNS disorders remain unresolved clinical problems. In some instances, medicine factors simply cannot pass the blood brain barrier (BBB) into the CNS (Pardridge, 2005). The appearance of nanomedicines can increase the transfer of biologically active molecules for aimed treatment and imaging. The field of nanoneuromedicine suggest real chances to harness unique therapeutic approaches to address diseases of the CNS where often few options exist, because of the enormous potential of the field. In addition to improved therapies, novel, more secure and more sensitive specific imaging conditions as well as better diagnostics for finding illness are instantly needed CNS disorders, due to infection, trauma or degenerative disorders; represent a significant societal burden with parallel broad unmet needs. In many and some cases, prevalent therapy are simply insufficient to modify illness progression or even improve signs of brain injury or degeneration. significant turbulency abound and are correlated with deliver of therapeutic or imaging opposition factors across the BBB into the CNS and hold the ability to get aimed transfer to proper brain or spinal cord subregions.

Nanomedicines can facilitate solutions to such problems. This case and relevant enabling technologies can enhance drug – drug interplay, simplify improving immunomodulation, enable pathogen rasure and ameliorate CNS transfer of biologically active molecules. Included are multifunctional therapeutic, imaging and diagnostic devices currently referred to as theranostics.

However, limitations for improved drug delivery to the CNS are not trivial, including the potential for secondary toxicities. Thus, any new formulation must balance a drug therapeutic index. This highlights a quite diverse and multifaceted field of research in biomarker discovery, bioimaging and theranostic (Gharib Salehi, 2016). If successful, therapies to address neurodegenerative, immune and infectious diseases of the CNS could be realized and more options would be available for human use (Ghannad, 2016). In this text, nanotechnology-based methods have reached great interest as a gadget in attempt to ameliorate the effectiveness of the imaging of CNS functions and disease states as well as to advance neurosurgical practice. Magnetic resonance imaging (MRI) has emerged as the most important tool in the diagnosis of brain disorders (Fatehi, 2016). Nanoparticles containing iron, gadolinium and manganese were studied extensively as contrast agents. Among them SPIONs have garnered interest due to their large surface area, magnetic properties and low toxicity. The BBB shows an impassable barrier for most medicines containing neurological drugs cytostatics antibiotics, etc. One efficient possibility to deliver drugs including peptides and even macromolecules across this barrier is the employment of polymeric nanoparticles. This possibility was recently summarized in a short review in this journal. Unfortunately, previous reviews frequently cite similar references and highlight similar points, often for studies that are repetitive or incremental over time. Focus on amazingly necessary pharmological effects attained with nanoparticles based transfer as well as perusal regarding mechanisms of nanoparticle intercede drug delicery are not often analyzed (Arruebo, 2007).

Mechanism of nanoparticle-mediated uptake of drugs into the brain: About eight possibilities exist for the mechanism of uptake of nanoparticles and of bound drugs into the brain including: an enhanced support of the nanoparticles in the brain blood arteriole combined with a sorption to the arteriole septum. This could make a higher condensation incline that would enhance the delivery among the indothelial cell layer and as a consequence increase the transfer to the brain. The polysorbate 80 used as the covering factor could prevent the current system, particularly P-glycoprotein (Pgp) that general toxic effect on the brain vasculature. A general surfactant result determined by the solubilization of the endothelial cell velum lipids that would lead to velum fluidization and to enhanced drug permeability across the BBB. Opening of the tight junctions between the brain blood vessel endothelial cells. The medicine could then infiltrate through the firm linkage in free form or altogether with the nanoparticles in closed form.6.endocytosis by the endothelial cells pursued by the extrication of the medicines within these cells and transfer to the brain. Transcytosis through the endothelial cell layer. As discussed in detail in a recent review, the nanoparticle intercede delivery among the BBB seems to happen by endocytosis of the particles by the brain arteriole endothelial cells after intravenous infusion followed by nanoparticle transcytosis across these cells. Earlier reviews already pointed out that mechanisms 1–6 appear to be of no major relevance: Making high medicine condensation incline by subordination of nanoparticles to the inner level of the blood arteriole septum (mechanism 1) would not be enough for an effective and pharmacologically relevant drug transport across the endothelial cell layer since the diffusing drug still would have been subjected to the highly efficient efflux transporters such as Pgp in the luminal membranes of these cells.

These current deliveries also cannot be cloged by the tendance of the 1% polysorbate 80 in the perfused nanoparticle pendency because the pre-injection of polysorbate 80-coated empty nanoparticles 5 or 30 min before injection of a dalargin solution did not induce any pharmacological effects. If current transporter dissuasion would have been the underlying mechanism, these transporters would have been inactivated by the polysorbate limited to the empty nanoparticles which then would have enabled the drug flux across the endothelial cells. The fact that pre-injection of polysorbate-coated empty nanoparticles did not achieve such a transport of drug in solution into the brain also refutes mechanisms and permeabilization of the BBB by toxic effects (mechanism 3) or by membrane

solubilization caused by the surfactant (mechanism 4) as suggested by Olivier and Calvo, also opening of the tight junctions (mechanism 5). This conclusion was further substantiated by electron microscopic studies, histological investigations, and toxicological experiments, which did not reveal any toxic effects at therapeutic levels. Additionally, a surfacetant induced permeability enhancement Seems to be improbable as no pharmacological replications seen after infusion of dalargin nanoparticles covered with other surfactants such aspoloxamers, poloxamine, Cremophor, and polyoxyethylene-laurylether.

The opinion that toxicity is not the mechanism for the nanoparticle-mediated drug transport across the BBB further was corroborated by the experiments of San, and of Koziara, Moreover, the electron microscopic studies by Zensi and by Kreuter, showed that the tight junctions (mechanism 5) did not open after intravenous administration of the nanoparticles. The latter result also is supported by the findings that no major increase in the inulin spaces was observable in rat brain perfusion experiments. Such an inauguration of the BBB could be attained for example by injection of hyperosmotic solutions and would enhance the inulin areas by a factor of 10-20. Consequently, mechanisms 6 and 7, endocytosis followed by transcytosis, are the underlying mechanisms for the transport of drugs across the BBB into the brain. In vitro perusal formerly clearly showed the endocytosis uptake of polysorbate 80 or poloxamer 188-covered nanoparticles into many primitive endothelial cells as well as into cell lines including mice and rat endothelial cell lines as well as primary bovine, porcine, and human endothelial cells. Similarly, an in vitro uptake also was observed into neurons and glioblastoma cell lines including A172 human glioblastoma cells (Kreuter, 2004).

To circumvent the BBB for the delivery of drugs to the central CNS, various strategies have been expanded such as the cutting of the BBB, chemical adjustment of the medicines to simplify velum penetrance and carrier or receptor-mediated medicine transfer. Further variant itinerary overrule the blood circulation altogether. For example, drugs can be delivered directly from nose to brain or delivered by intraventricular infusion. However, all these methods have limitations such as poor efficacy or invasivity. Thus, one of the major challenges of pharmaceutical research is to develop strategies for effective delivery of drugs to the CNS. To achieve this, an emerging approach is the use of nano-sized vectors such as liposomes and polymeric nanoparticles (NPs). Particularly, engineered NPs could take benefit of different directions for crossing the BBB, such as endocytosis or trancytosis. As shown in previous studies, we applied this approach by modifying Polylactide-co-glycolide (PLGA) NPs with a glycopeptide (g7) to make nanosystems (g7-NPS) that can enter the brain. Studies done in histological, biodistribution and pharmacological subjects have shown that g7-NPs cross the BBB at a high level following several modes of administration. Additionally, G7-NPs were found to educe endocytotic directions, both to cross the BBB endotheliul in vivo and to enter neurons or glial cells in vitro. in the attached paper (part 1), we focused on some other aspects, such as dose – time dependent accumulation of g7-NPs, tropism to specific brain regions and cell subpopulations after BBB crossing and constitution of relationship between in vivo and in vitro demodulations on the uptake mechanisms in neurons. Despite the findings gained on these topics, some subjects are still to be focused in depth to show an obvious picture of NP uptake, dynamics, deliver and trafficking inside the CNS. in particular, we have considered neuronal tendency the possibility of cell targeting using antibody (Ab) modified NPs, the possible transport of NPs from cell to cell and the dynamics of intercellular NP trafficking. In vivo, most cells can be found organized as specialized tissues. Within these functional assemblies, cells are able to perform cell to cell communication including the transport of intracellular components to organize physiological processes. Within the brain, neurons are closely surrounded by glial cells, leaving only a minimal amount of extracellular space. Thus, this part II study aims to evaluate the mechanisms of a possible intercellular transport of g7-NPs from cell to cell besides their transport within the extracellular fluid after crossing the BBB endothelium (Kreuter, 2002).

The CNS is composed of a dense network of neurons and glial cells that are highly interconnected. Thus, since these cells are not just a loose accumulation, but an organized tissue, cell-to-cell communication is an important factor for maintaining a functional organization. However, besides pairing of brain cells via gap-junctions, some other mechanisms may exist that can deliver internal as well as external cell components. Seong Deok Kong, have focused on the characterization of delivery of SPION to the brain parenchyma of normal mice with intact BBB. First, they demonstrate the delivery of SPIONs To the brain administrated by and external magnetic scope with minimal neurotoxicity. Second we determine obvious BBB. First they show the transportation of SPIONs to the brain administrated by an external magnetic scope with minimal neurotoxicity. Second, they show obvious BBB passing and extravasation of SPIONs induced by external magnetic force using cellular level high-resolution imaging analysis in vivo. Third, they show the transfer of nanoparticles in the CNS passing the sound BBB. their article instate the valency for the adjustment of CNS dispensation of SPIONs with the application of an external magnetic scope, showing passing of the BBB and accumulation in the perivascular space with no apparent toxicity, which can be beneficial for treatments of CNS diseases (Kreuter, 2001). They have planned and expanded fluorscent SPIONs and showed their potency in vivo to access the brain parenchyma by passing the normal BBB under the adjustment of an external magnetic scope. While the mechanism of BBB passing subsist unknown, their data indicate that the

endothelial membrane is capable of MNP uptake with kinetics that is consistent with the in vivo model. Their AFM results demonstrate that these SPIONs are spherical in shape and their average diameter is 124nm, which provide enough uptake by human brain endothelial cells. The fluorescence of the SPIONs enables their direct tracking and localization within specific vascular niches in the brain. Furthermore, the increased magnetic exclusivity and their replication to an external magnetic scope to simplify their extravasation and / or amplitude in the brain parenchyma support the idea of using similarly configured, medicine – containing magneticnanocapsules to deliver CNS drugs across an intact BBB. They demonstrate in this study the increased sensitivity to a magnetic field of engineered SPIONs compared to standard magnetic nanoparticles, and explore the capacity to use such SPIONs to access the brain parenchyma. They have focused on delivery across the intact BBB. Recent studies also demonstrate the usage of external magnetic field to facilitate the delivery of SPIONs across the BBB. In addition to these reports, their research demonstrates BBB translocation of SPIONs with higher resolution confocal analysis to pinpoint the extravasation of SPIONs in reference to the vasculature, which is supported by our histological analysis. Furthermore unlike in vitro BBB cell culture patterns with some restrictions, our in vivo pattern is more appropriate to discuss the multi – cellular intricate nature of BBB and pharmaco-distribution of SPIONs. Moreover, our information demonstrate that magnet – mediated transfer of SPIONs can happen in normal brain parenchyma without any vascular sprinkle as showed with the TRITC – 70 kDa dextran.

The internalization of SPIONs observed by the AFM imaging indicates that endocytosis or a non-specific membrane-mediated uptake of the SPIONs occurs, the mechanism underlying such uptake is unclear and beyond the scope of this study. Nevertheless, the decretive result of these studies is that MNP uptake into the brain does not seems to need a main infraction of the endothelial obstacle or change in BBB impeccability. Based on the valency to load such MNCs with medicines and the cell biological analysis with respect to BBB integrity, these SPIONs are ideal candidates to examine their relevance in translational models (Hernot, 2008). This is due to the significant challenge faced by industry and academics in seeking effective drug therapies for the increasing incidence of brain disease associated with an ageing population. In this review, we looked at the barrier issue from a biological and pathological perspective to provide a better insight to the challenges and opportunities associated with the BBB. We need to remind ourselves that we are developing drug delivery systems which ultimately will transport a drug to a diseased brain, not a healthy one. The delivery system, including the targeting ligands should be designed based on knowledge of the diseased BBB. To successfully target the brain, the selectivity of a BBB receptor is extremely critical. This means, ideally, the receptor should be brain specific, or at least, preferentially expressed at the BBB. Unfortunately almost all the receptors are nearly non-specific as shown by percentage dose reached the brain compared to that reached by the liver, spleen or lung. We believe that the reason for this high level of targeting is the design of the delivery system that is based on the pathological condition of the BBB and the fact that the system was tested on a diseased model.

The targeting effect was greatly enhanced further by its combination with the guidance of an external magnetic field. In contrast, while RMT worked alone, the best brain targeting, as far as authors are aware, was achieved by g7 molecule which was characterized as a high but short lived targeting (14% at peak). Unfortunately the majority only achieved 1–4% as a result of poor selectivity and low BBB permeability. Although the amount reaching the brain may be sufficient for a therapeutic effect, the loss of 96–99% is huge from the cost point of view, in addition to the potential side effects and toxicity that can be caused by 96% of drugs. Jones and Shusta suggest the solution may be in combinatory antibody library technology which allows the development of BBB-specific RMT. Tosi, showed that the application of double targeting ligands can provide added targeting benefit. These nanoparticles containing a fluorophore within have been engineered for direct tracking and measurement of the position of SPIONs, which also allow cellular-level high-resolution imaging analysis such as confocal microscopy (Kaittanis, 2007). Applied magnetic field facilitated the extravasation and/ or accumulation of these magnetic nanoparticles in the brain parenchyma. Similarly configured, but drug-containing magnetic nanocapsules can be utilized for BBB crossing and treatment of various CNS diseases. Use of multiple targeting ligands developed with consideration of the pathological conditions of the disease will maximize success. Ideally the treatment for a brain disease should be constantly monitored and modulated (Kennedy, 2011).

2. CONCLUSIONS

The idea of using magnetic or bubble filled and drug-loaded nanocarriers, in combination with MRI and ultrasound, may provide a solution for achieving both the diagnosis and treatment purposes (Chen, 2012). In conclusion, therefore, is to take the multidiscipline approach with innovative ideas to ultimately achieve the goal of delivering both diagnosis and drug therapy, selectively and efficiently, across the BBB. Our final conclusion is that any brain-targeted delivery systems must be assessed for their safety, risk and benefit for patients. Currently the safety issue has been largely overlooked during the research stage, yet this issue will become critical when the drug to be delivered is for a long term therapy. It is extremely important that any delivery systems developed should have no significant impact, short or long term, on the functions of the brain. The translation of NPs in clinical use for

therapeutic and diagnostics applications looks promising amidst the recent developments (Bohmer, 2009). The field of nano-pharmaceuticals is an emerging area of great medicinal interest, which aims at developing novel engineered nanoparticles for pharmaceutical applications and show great promise with varied range of usages such as in vaccination cell treatment and gene therapy. For example nanoparticle - based medicines attaining significant interest in pharmaceutical industry and already in clinical operation are liposomaldoxorubicin and albumin conjugate paclitaxel. In addition, many other NP based diagnostic and therapeutic agents are in clinical trials, and future looks promising for the fast growing field of nano-diagnostics. Moreover, further improvisations are needed to increase the translation of NP formulations from bench to clinics.

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