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Review Article

Carrier Systems to Pass Through Bbb-A Boon to Treat Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) is an autoimmune neurodegenerative disease characterized with immunopathobiological events, including lymphocytic infiltration into the Central Nervous System (CNS), microglia activation, demyelination and axonal degeneration. Although several neuroprotective drugs have been designed for the treatment of MS, complete remission is yet matter of debate. Therefore, development of novel therapeutic approaches for MS is of a high priority in immunological research. Nano-medicine is a recently developed novel medical field, which is applicable in both diagnosis and treatment of several cancers and autoimmune diseases. Although there is a marked progress in neuroimaging through using nanoparticles, little is known regarding the therapeutic potential of Nano-medicine in neurological disorders, particularly MS. Moreover, the majority of data is limited to the MS related animal models. In this review, we will discuss about the brain targeting potential of different nanoparticles as well as the role of Nano-medicine in the diagnosis and treatment of MS.

Keywords: Kratom; *Mitragyna speciosa*; Mitragynine; 7-Hydroxymitragynine; Poison Control center; National poison data system; Dietary supplement

Introduction

Multiple sclerosis (MS) is the most common neurodegenerative disease of the central nervous system (CNS) in young adults; it affects about 1 million people worldwide, with a higher prevalence in Europe and North America [1]. MS is a CNS-related disorder characterized by chronic inflammation, local demyelination, gliosis, variable axonal destruction and substantial immune cell infiltration [2]. Experimental autoimmune encephalomyelitis (EAE) is a widely used animal model of MS that has been induced via immunization with spinal cord homogenates, myelin or specific myelin peptides [3]. Despite several attempts to develop treatments for MS, effective drugs with fewer side effects are still needed [4]. Nano-medicine is a novel promising technology for treatment of various autoimmune disorders [5]. It has been shown that nanoparticles (NP) can be used in both the diagnosis and treatment of immune-pathologic diseases [6]. However, treatment of neurological disorders has usually been associated with several problems, including the blood–brain barrier (BBB) hindrance and a variety of side effects. In recent years, Nano-medicine has improved the efficacy of diagnosis and CNS-targeted therapy of several neurologic disorders. Nano-engineering has provided important diagnostic/therapeutic advantages. As only small lipophilic molecules can cross the BBB, the use of many therapeutic drugs has been associated with several problems. Nano-medicine may help to overcome this BBB impediment in treating neurologic disorders. The capability of NP to traverse the BBB improved the chances for early diagnosis and effective MS therapy [7]. This review discusses the role of Nano-medicine in brain targeting, diagnosis and treatment of MS.

Multiple sclerosis

Multiple Sclerosis (MS) is a complex heterogeneous neurologic disorder and various clinical symptoms, such as changes in sensation, visual problems, muscle weakness and difficulty in coordination and speech have been demonstrated in these patients. MS is characterized by demyelination and axonal loss mediated mainly through T-helper (TH) cells (particularly TH1 and TH17), macrophages and pro-inflammatory mediators. Although the etiology of MS is elusive, it seems that MS has an immune-pathological trigger arising from gene environment interactions. It is suggested that diet, sunlight, infections and genetics are of important etiologic factors in MS patients. Multiple sclerosis (MS) is classified into four types. The majority of patients (85%) show an initial relapsing remitting (RRMS) disease that may shift toward secondary progressive MS (SPMS). About 10% of MS patients exhibit primary progressive MS (PPMS) characterized by continuous disease progression. Relapsing progressive MS (RPMS), a rare form of MS, is characterized by disease progression from onset, which will be followed by continuous relapses [8].

In spite of promising advances in the understanding of MS pathogenesis, precise details about the neuro-inflammatory processes remain elusive. In general, MS is characterized by generation of acute inflammatory lesions initiated by breakdown of the BBB. MS lesions can be categorized into active/inactive and acute/chronic lesions. Despite the presence of a large numbers of macrophages in acute and chronic active lesions, the axons are usually intact. On the other hand, while a few macrophages are present in inactive plaques, loss of axons and oligodendrocytes has been observed in these lesions. In general, the acute and chronic active plaques are usually seen in RRMS and SPMS with relapses, while the inactive lesions occur in SPMS and [9]. The molecular mimicry and bystander activation following interaction of immune cells with foreign antigens are important factors in induction of MS [10]. It has been shown that auto-reactive T-cells that react with self-antigens of the CNS initiate and promote autoimmune responses against the CNS. T-cells (particularly TH cells) orchestrate cellular and humoral responses leading to neuro-inflammatory processes that damage myelin, oligodendrocytes and neurons. Dendritic cells (DC) that present self-antigens to auto-reactive T-cells play a crucial role in the induction of auto-reactive responses [11]. It seems TH1 and TH17 cells are the main pathogenic populations in the immune-pathogenesis of MS. Although there is no DC in a healthy CNS, other antigen-presenting cells (APC) like macrophages, microglia, B cells, endothelial cells and astrocytes can prime auto-reactive T-cells at the disease initiation stage [12]. Interestingly, it was reported that microglia and macrophages could differentiate into DC-like cells. It has been suggested that obstructed blood flow in narrow vessels lead to shear stress, which results in increased production of reactive oxygen and nitrogen species (oxidative stress) in endothelial cells. These reactive species enter astrocytes and increase oxidative stress. Accumulation of oxidative stress leads to activation of macrophages/microglia and induces apoptosis in oligodendrocytes. These sequential events may describe the initial stages of MS occurrence, suggesting a mechanism by which crosstalk between the circulation and the brain can lead to disruption of the BBB. It has been shown that there are a number of different myelin epitopes that act as self-antigens in MS [13] and oxidative stress may play an important role in the formation of these epitopes. Consistently, combination of malondialdehyde (MDA) with myelin oligodendrocyte glycoprotein (MOG) improves the phagocytosis of MOG by APC. Moreover, administration of MDA-MOG to mice leads to increased numbers of TH17 and TH1 cells, which are the most important cells in immuno-pathogenesis of MS. Notably, increased levels of MDA and MDA adducts have been detected in cerebrospinal fluid (CSF) of MS patients [14]. These data may indicate that myelin-derived self-antigens are not sufficient to induce auto-reactive responses and the presence of myelin-like immunogenic molecules such as MDA-MOG, 4-hydroxy-2-nonenal (HNE) and neuroketal-adducts, nitrosylated peptides or citrullinated-myelin basic protein (MBP) is crucial to induce autoimmune responses [15].

Methods

As described before, the oxidative stress damages myelin and releases myelin fragments, which are phagocytosed by microglia and macro-phages. These cells present self-antigens to CD4þ and CD8þ T-cells and facilitate their differentiation into activated auto-reactive cells. The micro-environmental factors such as osteo-pontin, interleukin (IL)-1, IL-12, IL-23, tumor necrosis factor (TNF)-a and other cytokines secreted by various cells such as astrocytes enhance the differentiation of CD4 TH cells toward TH1 and TH17 cells. Finally, the pro-inflammatory and cytotoxic mediators released by both TH and CD8 cytotoxic T lymphocytes enhance several self-reactive responses, which damage tissue. On the other hand, DC can collect myelin-derived fragments in the CNS and migrate into the lymph nodes. Following antigen presentation to auto-reactive T-cells by these DC, TH and CD8þ T-cells migrate into the CNS and damage tissue where this antigen is present. Oxidative stress enhances the secretion of differ ent cytokines and chemokines by astrocytes, which recruit leukocytes into the CNS. Specifically, H2O2 increases the expression of VCAM-1 and CCL2 on endothelial cells. Moreover, TH17-derived IL-17 enhances the generation of CCL20 and inhibits the expression of CXCL12 in the endothelial cells, which lead to increased leukocyte infiltration into the CNS [16]

During the last two decades, several studies have performed to introduce new therapeutic approaches for MS patients. Among the current MS drugs, interferon (IFN)-b was the first marketed [17]. Subsequently, glatiramer acetate was introduced as a MS drug, which affects antigen presentation and cytokine balance [18]. Fingolimod was the first MS oral drug, which inhibited T-cell migration [19]. Finally, teriflunomide and dimethly fumarate are the newest marketed MS drugs with evidence of efficacy. Almost all these drugs are mainly effective for relapsing forms of MS; however, the use of these drugs in MS patients is associated with variety of side effects. Currently, attempts to design new therapeutic agents in MS patients remain ongoing.

Nanoparticles and drug delivery into the CNS

The CNS physiologic barriers, including the BBB and the blood cerebrospinal fluid (CSF) barrier (BCSFB) limit access to the CNS for the majority of systemically delivered drugs, and hence ham per treatment. Although these barriers inhibit the systemic drug delivery into the CNS, they protect the CNS against infection and toxins. While the BBB is formed by tight junctions of capillary endothelial cells and the astrocytes, BCSFB consists of the tight junctions of choroid plexus cells encompassing the micro-vascular endothelium [20]. These barriers precisely control the transfer of molecules between the blood and CNS or CSF. The transfer of biologic molecules from blood into the CNS or CSF is through a trans-cellular pathway via the capillary endothelial cells or choroid plexus cells in passive and/or active dependent manner. Lipophilic molecules with the molecular weight <600 Daltons can usually cross the BBB and BCSFB. It has been shown that the essen-

tial nutrients such as amino acids, carbohydrates and nucleosides may cross BBB and BSCSFB through cellular transport systems such as receptors and carriers. Among these transport mechanisms, the natural transfer of macromolecules conjugated with surface receptor ligands like insulin, lactoferrin or transferrin is in a receptor-mediated manner. Moreover, cationic molecules and peptides such as albumin can pass across neurologic barriers through receptor-mediated absorptive endocytosis. There are also active transport systems such as system L-transporters, concentrative nucleoside transporter, P-glycoprotein, multidrug resistance-associated proteins, etc., that can transport different molecules into the CNS in adenosine triphosphate (ATP)-dependent manner [21]. The use of Nano-particulate carriers for drug delivery into the CNS has been studied and some of them such as poly(lactic-co-glycolic acid) (PLGA) are clinically approved that will be discussed. Nevertheless, the CNS-penetrating ability of NP makes them promising tools for early diagnosis of the CNS disorders [22]. Infiltration of NP into the CNS is related to their small size and surface features.

Micelles

Micelles exist as natural and synthetic polymers with size range from 2 to 20 nm, depending on composition and concentration. Polymeric micelles are composed of a hydrophobic polymer core (such as poly(propylene glycol)) and a shell of hydrophilic polymer blocks such as poly-ethylene glycol (PEG) [23]. The ability to make Nano-scale micelles through self-assembly in a specific solvent is the main feature of amphiphilic block copolymers. These Nano-scale micelles have been used as carriers in therapeutic systems [24]. Regarding the small size of these carriers, they can transport drugs across neurons to the brain via endocytosis [25] Polymeric micelles composed of Pluronic block co-polymers (also termed poloxamer) are effective carriers for hydrophobic drugs with long-circulating characteristics via inhibition of phagocytosis by the reticulo-endothelial system [26]. Pluronic block co-polymers are approved by Food and Drug Administration (FDA) for pharmaceutical and clinical applications and listed in the US and British pharmacopoeia as pharmaceutical excipients [27]. Following the deep, high delivery of Nano-formulations into the nasal cavity, they reach to olfactory mucosa and are transported into the brain and CSF through the olfactory receptor neurons. There are two feasible routes for Nano formulations to reach into the brain, including the olfactory nerve pathway (axonal transport) and the olfactory epithelial pathway. To overcome the BBB-mediated exclusion of brain-targeted drugs carbopol based gels are designed for nasal delivery of bio-pharmaceuticals [28]. Modified polymeric micelles were developed for effective drug delivery into the CNS. Zhang and colleagues were developed a transferrin-conjugated cyclo-(RGDFK)-paclitaxel micelle that could effectively transport drugs into brain *in vivo* [29]. The surface modification of micelles with cell-penetrating peptides (CPP) was another promising approach to specific CNS delivery of various micelles loaded with drugs. These CPP are cationic or amphiphilic peptides derived from Tat protein (from human immunodeficiency virus) and a Drosophila antennapedia homeo-protein that enhance intracellular delivery of drugs.

Nano-emulsions

Nano-emulsions are characterized as a system of water, oil and amphiphile, stabilized with a surface-active film. Films surround the water droplets at the oil/water interface and increase the stability of an emulsion by increasing the interfacial viscosity.

These films are created following the adsorption of high-molecular weight polar molecules that are inter-facially active (surfactant-like behavior). Oils that are rich in x-3 and x-6 poly-unsaturated fatty acids (PUFA) such as fish oils, flaxseed, hemp and wheat-germ oils can be used in the production of Nano-emulsions. Amphiphilic surfactants such as egg phosphatidylcholine and co-surfactant molecules including stearylamine, deoxycholic acid and dioleoyltrimethyl-ammonium propane (DOTAP) can be also applied for stabilization of these Nano-formulations [30]. Regarding their high loading efficiency, Nano-scale diameter and good penetration capacity, nano emulsions can be attractive devices in drug delivery into the CNS. As a drug carrier, they have several advantages such as effective encapsulation, sustained drug release and long circulatory times. It is suggested that if targeting moieties such as folate [31], thiamine, endothelial growth factor receptor (EGFR) binding peptide [32], mannose etc., to be anchored to the Nano emulsion, they can deliver their cargo with significantly higher efficiencies and remain longer at the disease site to allow for total transfer of the drug molecules. The size of Nano-emulsions is <500 nm in diameter; these can successfully incorporate poorly soluble drugs. Nano-emulsions release drug molecules through fusion of oil droplets to the biological membrane. There are several methods that can be applied for preparation of Nano-emulsions; however, high-energy emulsification method is preferred. High-energy emulsification approaches use mechanical energy that creates intense disruptive forces leading to the formation of tiny oil droplets. There are some Nano-emulsions commercialized by industries for biological and medical applications [33]. Moreover, there are some FDA-approved Nano-emulsion based formulations such as Camptosar and Fluosol that have been analyzed in MS patients [34]. However, Nano-emulsions have not been used for drug delivery to MS patients and this issue can be investigated in future studies.

Liposomes

Liposomes are spherical unilamellar or multilamellar lipid vesicles composed of one or more phospholipid bilayers with aqueous center. Therefore, they can readily encapsulate hydrophilic, amphiphilic and lipophilic drugs in their center or within the phospholipid bilayer. Although there are several methods for production of liposomes, the thin-film hydration or Bangham technique is extensively used which includes dissolution of the lipid in a biologic sol-

vent, solvent evaporation and the dispersion of the lipid film in aqueous media. Different type of liposomes can be applied for various purposes. Conventional liposomes usually contain neutral lipids (such as cholesterol, dimyristoyl phosphate-dylglycerol, dipalmitoyl phosphatidylcholine) and phosphatidylcholine. In addition to conventional liposomes, there are other types of liposomes such as stealth liposomes (sterically stabilized liposomes), cationic liposomes (amphiphilic molecules composed of a charged head connected to a hydrophobic anchor), archaeosomes (comprise the unique glycerolipids of Archaea), virosomes (unilamellar lipid envelops, derived from viruses), etc., which can be used for different goals. Furthermore, liposomes can also be functionally categorized into stimuli–responsive, pH-sensitive, thermo-sensitive, fusogenic and immunoliposomes that each one has its specific characteristics which let us to choice the best option for our different goals. The short circulating time (due to uptake by phagocytes and self-destruction) is one of the most important limitations of liposomes and can be improved in part through decreasing their size (<100 nm) or conjugation with PEG molecules (PEGylation). In general, nanocarrier systems with lower size have usually higher circulating time compared to large NP, however, this claim is not consistent for all nano formulations. The size of the liposome-based NP plays an important role in the clinical outcome. It is demonstrated that liposomes smaller than 100 nm in diameter exhibit a longer half-life in the blood and can evaded from the reticuloendothelial system compared to large liposomes. Similar results were observed when liposomes with the size 250 nm in diameter were compared with liposomes 100 nm in diameter with similar lipid composition. It has been shown that surface modification of liposomes including transferrin-modified liposomes, glucose modified liposomes GLU1000-LIP, Tat-conjugated liposomes and dual transferrin and folate-conjugated liposomes could increase their brain targeting. Thus, it seems that use of modified liposomes may be effective therapeutic approach in MS therapy.

Nanospheres and nanocapsules

Nanospheres are NP composed of a solid core surrounded by a dense polymer matrix, which is usually prepared through micro emulsion polymerization method and have sizes from 100 nm-1000 nm. Various drugs can be encapsulated, entrapped, dispersed, adsorbed or chemically attached to these NP. It is demonstrated that various materials such as collagen, gelatin, chitosan, fibrin, alginate, poly-(a-hydroxy-esters), such as poly-(lactic acid) (PLA), poly-(glycolic acid), PLGA and poly-(caprolactone) (PCL), are the most frequently used synthetic polymers for generation of nanospheres. Among them, PLGA is a commonly used and only FDA-approved compound that exhibits low toxicity and high efficiency compared to the other compounds. Little is known about the efficiency of nanospheres in treatment of neurological disorders. Wolfhart and colleagues demonstrated that surfactant coated doxorubicin loaded nanospheres could effectively cross the BBB and reach to the brain parenchyma in animal models. Regarding the existence of limited information, nanospheres should be investigated in a variety of pathologic conditions. Nanocapsules are characterized with oil-filled cavity surrounded by a thin polymeric envelope (core-shell structure) and have sizes ranging from about 10 to 1000 nm. Several compounds such as hydroxypropoxy-methyl-cellu-lose, hydroxypropyl-methyl-cellulose, gum arabica, phthalate, diacyl-b-cyclodextrin, poly-(e-caprolactone), poly-(D,L-lactide), poly-(alkylcyanoacrylate), vegetable or mineral oils, ethyloleate and benzyl benzoate can be used for production of nanocapsules. Moreover, both hydrophilic (laryl sulphate, quatery ammonium, or [poly-(oxyethylene)-poly 72-(propylene) glycol]) and lipophilic (natural lecithin) surfactants stabilize the nanocapsules. Altogether, nanospheres and nanocapsules demonstrate several advantages such as high drug loading, high circulation time in plasma, ease of surface modification and high resistance against reticuloendothelial system. The nanosphere based Verigene system is approved for the identification of influenza A, influenza B and respiratory syncytial virus from nasopharyngeal swab specimens placed in viral transport media. Although the neuroprotective function of these NP has been shown *in vitro*, little is known regarding their efficacy *in vivo*. However, it seems that these NP with some surface modifications may be the promising tools in the CNS drug delivery in MS patients.

Polymeric NP

Polymeric NP (PNP) is comprised of natural (e.g. albumin, gelatin, chitosan, poly-saccharides) or synthetic (e.g. polyacrylamide, e-poly-caprolactone, polyacrylates) polymers. Based on the preparation process, PNP may appear as nanospheres or nanocapsule structures with sizes ranging from 100 to 1000 nm. Various PNP, including PLGA, chitosan, polybutyl-cyanoacrylate (PBCA), PCL, PLA, polyglycolide, poly-(D, L-lactide) and PLGA–PEG have been used for drug delivery for the treatment of different immunopathologic conditions. Among the PNP found, PLGA, PLA and PCL have been approved by the FDA for human use. PLGA NP has high capacity to protect their cargo from degradation and prolong the release of therapeutic agents, so they have been used in several pre-clinical studies for treatment of various diseases, particularly cancer. PLA NP is homo-polymers that are more crystalline compared to PLGA. Although it is evident that the more attention has been focused on PLGA compared to PLA, it is difficult to say PLGA is better than PLA. PNP can be classified as biodegradable or non-biodegradable. Biodegradable NP exhibit several advantages, including high stability and less immunogenicity. These NP are biocompatible and do not stimulate any inflammatory response. The high capacities of these NP for entrapping both hydrophilic and hydrophobic drugs along with excellent release profiles have made them promising tools for drug delivery systems. Several studies have demonstrated the CNS drug delivery through various PNP such as PBCA.

Regarding the low BBB transmission efficiency, surface modification of these NP with molecules such as antibodies, surfactant or transferrin can make them potent carriers

for drug delivery into the CNS. Anti-transferrin receptor antibody conjugated PNP could effectively deliver drugs such as methotrexate, proteins like basic fibroblast growth factor, nerve growth factor and brain-derived neurotrophic factor into the CNS. Although, there are some FDA approved PNP such as Carmustine for glioblastoma multiform, Risperdal Consta for schizophrenia and Abraxane for mammary cancers, there is no PNP-based therapeutic approved for the diagnosis or treatment of MS. Moreover, there are only a few pre-clinical studies that have tried to test the efficiency of PNP in drug delivery into the CNS.

Solid lipid NP

SLN (or lipospheres) are composed of solid lipids, including tri-glycerides, waxes or complex glyceride mixtures stabilized by surfactants, with an average diameter between 10 and 1000 nm. Among the various techniques used for production of SLN, high-pressure homogenization at high temperatures and microemulsion are the most applied methods used for SLN generation. These NP have several features such as high stability and tolerability, gradual drug release, specific targeting and protection of labile drugs from degradation. However, SLN show some limitations such as low drug-loading potential and drug leakage. Lipid drug conjugates (LDC) and nanostructured lipid carriers (NLC) are improved SLN that have additional advantages compared to SLN. The main purpose in the development of LDC is to improve the compatibility of lipid based carriers to lipophobic molecules. NLC are lipid carriers containing a certain structure for the increased payload capacity and prevention of drug expulsion. Accordingly, it was shown that NLC could be classified into three types based on their lipid matrix structure, e.g. imperfect type, multiple types and amorphous or structure less type. The imperfect type has the lowest oil content and exhibits a defected lipid matrix and compartments for drug storage that leads to drug expulsion. Increases in liquid phase lipids in the multiple types of NLC inhibit drug expulsion. This type of NLC exhibits a higher drug loading and faster drug release compared to other NLC. Use of lipids such as hydroxy-octacosanyl-hydroxystearate and isopropyl-myristate leads to preparation of the amorphous type that lacks a crystalline structure and avoids drug expulsion. SLN exhibits several features such as evasion from the reticulo-endothelial (SLN in range of 120–200 nm), high stability, high drug loading efficiency, high reproducibility, incorporation of both hydrophilic and hydrophobic drugs and simple production on large scale, that make them potent candidate for drug delivery into the CNS. As a result, SLN have been used to deliver several therapeutic agents such as doxorubicin, atazanavir, quinine, docetaxeland quercetin into the brain, as described in previous studies. Regarding the lipidic properties of SLN, it is expected that SLN easily enter into the brain tissues. Because SLN are biodegradable, they show very low toxicity. As such, they were originally thought to be promising candidates for drug delivery into the CNS. Moreover, it has been reported that surface modification of SLN with targeting molecules such as galactosylation or folate enhanced their specific action. Thus, the addition of CNS-targeting molecules to SLN may increase specific drug delivery in neurological disorders. In line with this, it was reported that conjugation of SLN with transferrin or thiamine was associated with better outcomes in the treatment of cerebral malaria and increased brain uptake of drug, respectively. Although several SLN nano-formulations have been tested in pre-clinical studies, and some of them – such as Nanobase and Nanopearl – were approved by the FDA, there are still no marketed SLN-based nano-formulations for neurologic disorders, particu larly MS.

Dendrimers

Dendrimers are nanosized (1–100 nm) spherical compounds with repetitively branched structures. There are several types of dendrimers, including PAMAM, poly(propyleneimine) (PPI), poly-L-lysine, melamine, triazine, poly(glycerol), poly[2,2-bis(hy-droxymethyl)propionic acid] and poly-(etherhydroxylamine). However, PAMAM-type dendrimers have been studied more than other types as they have been commercially available for the longest period from different companies and have advantages compared to the other types. The high versatility of dendrimers has introduced them as potent nanocarriers in the CNS drug delivery. However, their three key features including monodispersity, their multivalency and their globular shape make them as potent nanotheranostic devices in biomedical fields. Both *in vitro* and *in vivo* studies have demonstrated the low toxicity and high CNS drug delivery of dendrimers. Due to their small size and highly packed surface functionalities, the functional groups can lead to synergistic effects of interacting with other biomolecules, i.e. poly valency. This multivalency led to the formation of various commercialized dendrimers, Starburst, Astramol, Polylysine poly-L-lysine and dendrimer-based products such as Vivagel, Stratus CS, Superfect, Dendrimer-docetaxel, Dendrimer-oxaliplatin, NB-001 and NB-002.

Nanogels

Nanogels are nanosized polymeric microgels composed of a network of charged poly-ionic residues attached to PEG molecules, which can effectively encapsulate various types of oligonucleotides and charged molecules. Nanogels are composed of a crosslinked hydrophilic polymer network, known as hydrogel, with sizes the tens to hundreds nm in diameter. Chemically or physically cross-linked synthetic polymers or biopolymers, such as dextran and polyethylenimine (PEI), are usually constitute to generation of nanogels. Different nanogels can be used for different purposes. For example, PEI-derived nanogels can be used for anti-cancer drug delivery, whereas dextran derived nanogels are applied for imaging tumor-associated macrophages with radionuclides and targeting the bone. Nanogels demonstrate several advantages as drug carriers such as high drug loading potential, dispersion stability, stability following freezedry process and ease of drug for mulation. The ionic interactions between negatively charged oligonucleotides and positively charged amines of PEI molecules in cationic nanogels are usually formed spontaneously during some minutes.

Carbon nanomaterials

It has been shown that carbon nano-formulations can be used for various applications such as cancer diagnosis, imaging, targeted photothermal therapy, photoacoustic imaging, drug delivery and tissue engineering. Carbon NP can be classified into two groups, including carbon nanotubes (CNT) and carbon nanohorns (CNH). CNT which are one dimensional graphitic material with unique structure, thermal and electrical features can be categorized into two subsets including single walled and multi-walled CNT, with diameters of 1–2 nm and lengths from 50–1000 nm. Various methods such as arc discharge, laser ablation, high pressure carbon monoxide disproportionation and chemical vapor deposition are used to produce CNT. It has been suggested that surface modification of CNT with PAMAM dendrimers can improve their biocompatibility and function. Moreover, conjugation of targeting molecules such as EGF onto CNT was also associated with selective action of these nano-formulations, *in vitro*. Chemical adsorption and especially encapsulation are common methods used for drug loading in CNT. A combination of carbon NP and magnetic NP is also proving to be a novel promising approach for biomedical applications. Their combination has been showed a synergistic effect; however, these joint usages still need to be investigated in further studies. It seems that for any clinical application of carbon nanomaterials, several lines of pre-clinical as well as trial studies are clearly necessary.

Discussion

Diagnosis

One of the important issues in the treatment of MS patients is determination of disease stage and neuroinflammatory process. Therefore, we need potent tools to investigate the precise immunopathologic condition, before treatment initiation. As mentioned previously, different immune cells can infiltrate into the CNS and induce neuroinflammation. Although immunohistologic assays can present precise data regarding the nature of lesions, their resolution is limited to small lesion area at one time. On the other hand, using magnetic resonance imaging (MRI), one can follow lesion generation and development over time in several areas. However, non-specific proton changes arising due to non-neuro-inflammatory processes may alter signals resulted by T2-weighted MRI. Identification of NP led to improving novel imaging methods, which allow us to specifically detect cellular dependent neuroinflammatory process in the CNS. The gold NP-dependent biobarcode technique is a potent amplifying method to detect very low molecular signals in CSF of neurologic disorders. Since a few radio diagnostic approaches are available for detection of MS lesions, including MRI, SWIP, application of such a NP-based methods able to detect and quantify ultralow signals in MS lesions could be useful in MS monitoring. Super-paramagnetic iron oxide particles (SPION) can also be useful in therapeutic approaches through their surface modification. Conjugation of environmental stimuli-sensitive polymers on the surface of paramagnetic polymers can make them useful as therapeutic devices. These therapeutic paramagnetic NP are known as ‘‘Smart’’ SPION. Different MS drugs such as IFNb can be loaded in smart SPION using these surface conjugated poly-mers. The different environmental conditions in normal and inflamed tissues, for example the lower pH in inflamed tissues, can be used a drug-release mechanism for injured tissues. Several stimuli-sensitive polymers such as triblock-poly(styrene-block2-vinylpyridine-block-ethyleneoxide), poly(vinylmethylsiloxane), poly(N-isopropylacryla-mide), polystyrene-poly(methylmethacry-late) and polystyrenepoly(methylmethacrylate) can be used for surface conjugation with SPION. Proteinticles are other useful tools in the diagnosis of MS. Proteinticles are nanoscale particles with constant structure and surface topology, which are self-assembled inside cells. Through addition or insertion of different peptides in different regions of these particles, several functional proteinticles can be easily synthesized.

In spite of several diagnostic and therapeutic advantages of paramagnetic NP in MS, it is suggested that the use of these NP may change the physiologic function of labeled cells and MS clinical outcomes. There are other novel NP-based monitoring approaches, such as bioconjugated tau protein AuNP, multipartite NP and quantum dots (QD) that show investigation in this field is ongoing and calls for further studies.

Conclusion

Drug delivery into the CNS is the most prominent problem in treatment of MS. However, recent advances in development of various nanoscale materials, which have high capacity in targeted drug delivery have opened new window in treatment of the CNS-related diseases such as MS. As mentioned, nanomedicine could be useful in MS through different ways, including neuroimaging (diagnosis), drug delivery and nanosurgery. Cationic NP may penetrate BBB better than anionic NP. Moreover, it was reported that conjugation of NP with molecules such as monoclonal antibodies (OX26, 8D3 and 83-14), CCP, thiamine, transferrin, folate, glycosides could specifically conduct NP toward the CNS. Unfortunately, the majority of studies are limited to EAE animal models and little in known regarding the therapeutic efficacy of NP in MS. Thus, before designing any NP-based therapeutic methods for MS patients, more investigations are necessary.

Conflict of Interest Disclosure

We declare that we have no conflicts of interest related to the authorship or publication of this manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon request.

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