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ARTICLE

Applicability and sanitary regulation of nanomedicine in major Central Nervous System (CNS) disorders

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ABSTRACT

In nanomedicine the nanocarriers are generally biocompatible, biodegradable with rapid biodistribution in the body and can be used to carry drugs or therapeutic genes. Thus, new drug delivery systems have been heavily exploited in the treatment of CNS disorders such as Parkinson's, Alzheimer's and glioma, since the CNS is a major challenge for therapeutic approaches due to the blood-brain barrier (BBB) and blood-cerebrospinal fluid (BCSFB). Thus, the scientific community together with government and private industry has added efforts to generate new formulations in nanoscale in order to achieve an appropriate therapeutic approach, satisfying, and that is within the principles of health monitoring for cerebral affections. This article aims to summarize the knowledge about the main barriers to drug delivery to the CNS, Nanomedicine, Glioma, Parkinson's, Alzheimer's and sanitary surveillance.

KEYWORDS: Nanomedicine; Central Nervous System; Glioma; Parkinson's Alzheimer's; Sanitary Surveillance

Introduction

In recent years, significant progress has been made in the field of nanotechnology, particularly in the areas of material science, supramolecular structures, drug delivery, and photodynamic therapy. In general, drugs are carried through nanoparticles (NPs), a term applied to particles with a size ≤ 100 nm. However, whether drugs and other substances up to 300 nm can also be considered within the nano range remains controversial considering their characteristics. In the therapeutic use of nanotechnology (usually termed nanomedicine), NPs are typically biocompatible, biodegradable, and rapidly distributed in the body. NPs have also been termed as nanocarriers because of their ability to transport therapeutic drugs or genes. A major advantage of NPs is the potential to increase their specificity for target tissues by up to 1,000 times. In the past, NPs were considered "magic bullets" that target only diseased cells or organisms of interest. During this period, their association with monoclonal antibodies was used to enhance their specificity; this association still exists but at a very high cost. Since then, new strategies such as nanocarrier systems have emerged.

Over the past three decades, there has been a major boost in the development of several nanocarriers capable of delivering specific drugs for various diseases such as neurodegenerative disorders, i.e., those that affect the central nervous system (CNS). These nanocarriers generally fall into distinct categories, including liposomes, albumin-bound NPs (nab® patented technology), polymeric NPs, dendrimers, and metallic NPs[1,2,3,4].

Various biodegradable nanocarriers conjugated to monoclonal antibodies, peptides, proteins, nucleic acids, and growth factors, among others, have been explored for the treatment of CNS disorders such as Parkinson's disease, Alzheimer's disease, glioma, psychiatric disorders, and pain disorders because nanocarriers not only arrest disease progression but also restore damaged cells. Furthermore, there is great interest in these biotherapeutic agents because of their efficacy, potency, and ability to reduce the side effects caused by active principles[2,5,6].

However, few organic products developed for the treatment of CNS disorders have attained clinical success, mainly due to the lack of drugs with properties of good solubility, *in vivo* stability, efficient penetration throughout the CNS, and low manufacturing cost, thereby limiting their entry into the market[7,8]. Thus, the scientific community, together with government institutions and private industries, are joining forces to create new carrier formulations at a nanometric scale in order to achieve an adequate and satisfactory therapeutic approach for brain diseases.

Main barriers to drug delivery to the CNS

The CNS represents a major challenge for therapeutic approaches because in contrast to other systems of the body, it is particularly impervious to foreign endogenous or exogenous substances. In this sense, the main obstacles encountered during drug delivery to the CNS are the blood–brain barrier (BBB) and the blood–cerebrospinal fluid barrier (BCSFB). The BBB comprises multiple cell types, including endothelial and microglial cells, astrocytes, and pericytes of the CNS, whereas the BCSFB comprises epithelial cells of the choroid plexus.

The BBB is the interface between the brain and blood vessels and is composed of endothelial junctures that control the opening and closing of intercellular bridges, such as tight junctions and adherent endothelial junctions. These junctions are key regulators of cell permeability and form a physical and metabolic barrier *per se*[9,10]. Therefore, the BBB prevents macromolecules from crossing the intercellular bridges that line the cerebrovascular system and blocks approximately 98% of potential drugs from reaching their targets in the CNS[7].

The BCSFB is the second barrier for systemically administered drugs before entering the CNS. Similar to the endothelial barrier, BCSFB comprises unique apical tight junctions that occur between the epithelial cells of the choroid plexus. These junctions are arranged in a manner that selectively directs the transport of ions, nutrients, and cells to the cerebrospinal fluid (CSF) and are responsible for removing toxic substances from the CSF[9,10].

The presence of such barriers in the CNS has great clinical implications and makes drug delivery to intracranial regions even more challenging during the treatment of brain tumors and neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. At present, therapies targeted at brain diseases often depend on vascular injury and permeability of the BBB and BCSFB barriers for their success. In contrast to primary and secondary systemic tumors, which are responsive to chemotherapeutic agents administered through the cardiovascular system, intracranial metastases are not affected by these agents and often continue to grow[11,12].

Nanomedicine for the glioma

Cancer is the uncontrolled growth of abnormal cells that have a tendency to be aggressive and can result in the formation of tumors or malignant neoplasia[13]. Glial tumors, generally known as glioma, are the most common CNS neoplasms in adults and are generated from astrocytes, oligodendrocytes, and their precursors. Histologically, gliomas can be classified into several groups; however, the two main types are oligodendrogliomas and astrocytomas[14].

According to the World Health Organization, oligodendrogliomas are slow-malignancy and slow-growth tumors that mainly occur in the white matter of the brain. The degree of malignancy is generally grade II; however, it may increase during relapses and become anaplastic oligodendrogliomas (grade III). Anaplastic oligodendrogliomas comprise tumor cells with round and homogeneous nuclei and are characterized by increased mitotic activity, microvascular proliferation, and necrosis[15]. Astrocytomas are categorized according to the degree of malignancy and aggressiveness as follows: pilocytic astrocytoma (grade I), diffuse astrocytoma (grade II), anaplastic astrocytoma (grade III), and glioblastoma multiforme (GBM) (grade IV)[15,16].

GBM is the most aggressive and common type of oligodendroglioma. It is usually found in the frontotemporal region but may also affect the parietal lobes. Some distinct features of GBM are nuclear atypia, rapid growth, microvascular proliferation, necrosis, genetic instability, and resistance to chemotherapeutic agents[17], all of which may lead to an unfavorable prognosis and an average survival of approximately 1 year for all affected patients[16,18].

GBM is subdivided into primary and secondary forms, can affect people of different ages, and can develop through different mechanisms. GBM forms are indistinguishable histologically but differ genetically and biologically. Primary GBM is the most common type and accounts for 90% of cases. In addition, it affects people aged over 60 years and develops quickly, without any clinical evidence of precursor malignant lesions. Secondary GBMs are established through the progression of low-grade gliomas (e.g., diffuse or anaplastic astrocytomas) and affect people aged over 45 years.

Because these tumors appear in the CNS and affect brain structures, patients with gliomas commonly develop symptoms that include headaches, seizures, vomiting, and papilledema as a result of increased intracranial pressure exerted by the tumor and edema. Seizures, neurological disorders with loss of sensory, mental and/or motor functions, and memory problems are also common in these patients[19].

Most gliomas are difficult to treat because of their invasiveness and resistance to conventional therapy. Even benign neoplasms with abnormal cells that do not infiltrate the adjacent CNS tissue can pose risks to patients because these neoplasms are difficult to treat and have a high proliferative rate. The therapeutic approach for newly diagnosed malignant gliomas has essentially remained unchanged for decades and consists of the surgical removal of the tumor mass as much as possible, followed by concomitant radiotherapy and chemotherapy with temazolamide (TMZ)[20,21].

GBM is highly resistant to chemotherapy because its abnormal cells have a high capacity for DNA repair. GBM is also characterized by the presence of multiple cells at different stages of the cell cycle (not only in the G2/M phase) and by the occurrence of several hypoxic areas with chemoresistant cells. The BBB reportedly hinders the delivery of drugs to the CNS[22].

In this sense, polymeric NPs are good candidates as carriers of drugs and contrasting agents, the latter of which have been used for diagnostic purposes such as real-time magnetic resonance imaging. In this sense, Bernal et al.[23] have used an iron oxide NP charged with the antiglioma drug TMZ, and this application resulted in brain tumor reduction and increased survival of experimental rodents.

Ling et al.[24] developed a superparamagnetic NP based on poly (D,L-lactic-co-glycolic acid (PLGA)). This NP was charged with TMZ and coated with polysorbate-80 (P80-TMZ/SPIO-NPs), and the uptake of this formulation significantly increased in an experimental model *in vitro* using C6 glioma cells.

Nanomedicine for Parkinson's disease

Parkinson's disease is a chronic neurodegenerative disease that affects the CNS, particularly the motor system. Although the causes of this disease are not completed understood, it is known to result from the degeneration and death of dopaminergic neurons in the gray matter of the brain. These neurons are responsible for producing the neurotransmitter dopamine, which is important for movement control[25,26].

According to the United Nations (UN), at least 4 million patients in the world suffer from Parkinson's disease. In Brazil, the exact number of people with the disease is not known; however, the Ministry of Health estimates that at least 200,000 people are affected. The global prevalence of Parkinson's disease is approximately 160 cases per 100,000 inhabitants, and the annual incidence rate is approximately 20 new cases per 100,000 inhabitants[27]. Both the prevalence and incidence increase with age and are higher in people aged over 50 years. Considering the increase in life expectancy of the population, projections for 2030 indicate that 9 million people worldwide will suffer from Parkinson's disease[28].

The diagnosis of Parkinson's disease is based on the presence of the most common vasomotor symptoms, including tremor, muscular stiffness, chronic constipation, impaired bladder emptying, and postural changes. Other nonmotor symptoms also manifested by patients include memory impairments, depression, sleep disorders, and disorders of the autonomic nervous system [26]. The definitive diagnosis is made on the basis of the presence of Lewy bodies in the substantia nigra, which are spherical structures with 8 to 30 µm in diameter that show a reddish color when stained with hematoxylin and eosin[29].

Although there is no cure for Parkinson's disease, its pharmacological treatment is based on significant improvements in symptoms to delay progress of the disease and can also involve the use of medication and nonpharmacological methods such as physical therapy[27,30]. At the early stages, treatment may be performed with an inhibitor of monoamine oxidase type B (MAO-B) or a dopamine agonist such as bromocriptine, lisuride, pramipexole, ropinirole, and pergolide, and in more advanced cases, the administration of levodopa or di-hydroxyphenylalanine (L-Dopa)[30] is recommended.

L-Dopa is the most effective therapeutic agent for the treatment of Parkinson's disease. Due to the inability of dopamine to cross the BBB, the precursor L-Dopa is used, which is converted to dopamine after decarboxylation by the enzyme dopa-decarboxylase[27]. Although L-Dopa is considered to be the reference drug to relieve symptoms, it is indicated only in the most advanced cases of the disease because its prolonged use can cause adverse reactions, which are caused by the conversion of most of the L-Dopa (approximately 95%) to dopamine by enzymes present in organs other than the brain. Because dopamine has peripheral effects, it can cause nausea and vomiting, tachycardia, mydriasis, agitation, insomnia, hallucinations, and abnormal involuntary movements known as dyskinesia[27,31]. Dopa decarboxylase inhibitors such as carbidopa and benserazide are

co-administered with L-Dopa to prevent its conversion before entering the brain and thereby reduce its undesirable effects[30].

A workaround for the problem of drug delivery is to develop a delivery system capable of carrying and directing L-Dopa to the brain, thereby avoiding the use of Dopa decarboxylase inhibitors. For this purpose, the therapeutic approaches based on nanomedicine have shown the most promising results. As an example, we can refer to the work of Trapani and colleagues[32], who observed higher levels of dopamine in the brain and a lower cytotoxicity after the intravenous administration of dopamine NPs to mice than that after the administration of dopamine alone.

In this sense, the Center for Nanotechnology, Tissue Engineering and Photoprocesses oriented to the Health - Group of Photobiology and Photomedicine at *Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto - Universidade de São Paulo*, Ribeirao Preto, state of Sao Paulo, has developed, in partnership with the Universidade de Brasília and Santa Casa de São Paulo, very interesting and promising systems for treating and preventing the spread of Parkinson's disease. Still in the animal phase, these studies have used drug delivery systems produced and patented by the Universidade de São Paulo in 2006, and these systems can traverse the BBB more efficiently than conventional therapies, thereby preventing the spread of disease.

The success of these studies propelled the idea of designing a synergistic system for the treatment of glioma, whereby the combination of a chemotherapeutic drug and a photoactivatable drug would reduce tumor size and concomitantly allow more precise procedures with much smaller surgical margins and less tissue damage around the tumor area, similar to what is clinically used for the treatment of skin cancer, with photoactivation of natural drugs that help eradicate the remnant cancer cells. These studies indicate that nanotechnology, photoprocesses, and tissue engineering can work together for the benefit of human health.

In the area of gene therapy for the treatment of Parkinson's disease, NPs have been used as vectors to deliver therapeutic genes in substitution for viruses such as retrovirus, lentivirus, and adenovirus, with the aim of reducing the mutagenic potential and the immune response. Using this therapeutic approach, Huang et al.[33] have demonstrated increased levels of dopamine in the brain of rats, a significant improvement in motor activity, and reduced neuronal loss.

Nanomedicine for Alzheimer's disease

Among neurodegenerative diseases, Alzheimer's disease is the most common disease in individuals aged over 65 years, and genetics has been considered as the major factor in the pathogenesis of the disease. Alzheimer's disease is an epidemic, with an estimated 33.9 million people being affected by the disease, whereby cognitive and neuropsychiatric manifestations result in progressive disability and may ultimately lead to incapacitation[34,35]. Usually, the first symptom is the impairment of recent memory, followed by the impairment of attention and verbalization, whereas old memories are preserved in the early stages of the disease. Other cognitive functions may progressively deteriorate and are accompanied by other behavioral disorders as the disease progresses, including aggression, apathy, hallucinations, hyperactivity, irritability, and depression[36,37].

Alzheimer's disease is histopathologically characterized by a massive synaptic loss and neuronal death in the cerebral cortex, hippocampus, striatum, and ventral entorhinal cortex, which are brain regions responsible for cognitive functions. Alzheimer patients may also have fibrillar amyloid deposits, senile plaques, and neurofibrillary tangles (NFT) in the walls of blood vessels in the parenchyma, in addition to neuronal and synaptic loss, inflammation, and glial activation.

Despite recent discoveries, little is known about the pathogenesis of Alzheimer's disease. Therefore, two hypotheses have been developed for the onset of neurodegeneration in Alzheimer's disease: the amyloid cascade, which begins with the proteolytic cleavage of the amyloid precursor protein (APP) and results in the production, aggregation and deposition of the ß-amyloid (Aß) substance and senile plaques, and the cholinergic system dysfunction, which is characterized by the degeneration of cholinergic neurons and decrease in the activities of the cholinergic markers choline acetyltransferase and acetylcholinesterase in the cerebral cortex of Alzheimer's patients[38,39].

It is postulated that the use of appropriate biomarkers could enable the identification of pathological features of Alzheimer's disease before the development of neuronal damage or early onset of symptoms; thus, treatment can be initiated as early as possible. At present, there is no cure for Alzheimer's disease and the preventive treatments available are aimed at slowing disease progression and minimizing symptoms. The drugs available for treatment are donepezil, galantamine, rivastigmine, and memantine, which act by preventing the decrease in the levels of the synaptic neurotransmitter acetylcholine or the formation of Aß plates[40,41]. Meanwhile, it is estimated that more than 400 new medicines are under investigation in approximately 1,100 human clinical trials (ClinicalTrials.gov, 2013) in addition to several other substances that are being tested in animal models. These new drugs are designed to reach central regions of the affected brain and thereby effectively cross the BBB[41,42].

Among the nanodrugs targeting the amiloidal cascade, we highlight some nanoencapsulated anti-Aß antibodies because of their high bioavailability and longer persistence in the circulation, such as curcumin, which inhibits the formation of Aß plaques and decreases amyloid levels *in vivo*[43]. Mulik et al.[44] observed that curcumin NPs caused a 40% reduction in Aß-related cytotoxicity, when surrounded by apolipoprotein E (ApoE), a ligand for the BBB receptor. Moreover, Matthew et al.[45] observed that curcumin NPs conjugated with the Tet-1 peptide, which has affinity for neurons, bypass the BBB and reach target neurons.

With respect to the cholinergic system dysfunction, carbon nanotubes have been used to overcome the short half-life of acetylcholine and facilitate its penetration through the BBB[46]. Notably, rivastigmine NPs coated with Polysorbate-80 can absorb ApoE from the bloodstream and more easily traverse the BBB, resulting in improved learning and reduced memory loss.

This same formulation has shown a 12-fold greater penetration compared with uncoated rivastigmine NPs tested in mice[47].

Nanomedicine from the perspective of health surveillance

According to prospective data, nanomedicine ranks second in the industrial sectors that are impacted by nanotechnology in Brazil, trailing behind the electronics and communications sector[48]. In this sense, research in the field of nanomedicine has been identified as an area of great potential not only to meet the demands from the Unified Health System (UHS) but also to meet the millennium goals of the UN, which include the mapping and diagnosis of diseases, drug delivery systems, and health monitoring[49].

With regard to the drug delivery system, it should be noted that at present, there is a shortage of effective therapeutic approaches for diseases affecting the CNS and these approaches do not reach the demands of the SUS, suggesting that research should be directed to this area and included in the proposed research priorities in public health[50].

Therefore, the development of a national policy for health research, including research on CNS disorders, must include the implementation of strategic programs prioritizing therapeutic approaches and must consistently incorporate health surveillance principles in its scope. Although the National Health Surveillance Agency (ANVISA) primarily aims to regulate products and services, this agency must include the scientific area and regard this area as a component of collective health[51,52,53].

For setting guidelines for the nanotechnology research to create a culture of innovation and progress for strengthening public health and regulating nanotechnology in Brazil, ANVISA has recently promoted the seminar entitled "Technological Innovation in Health: Challenges for Health Regulation" in Brasilia, Federal District, when the agency discussed the main issues related to nanotechnology applied to healthcare, with a primary focus on the conceptual aspects, applications, benefits, potential risks, challenges, and the implementation of more effective regulatory models[54]. One of the scientific groups that have been developing products for healthcare and attended the event is the Center for Nanotechnology, Tissue Engineering and Photoprocesses oriented to Health - Group Photobiology and Photomedicine at *Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto - Universidade de São Paulo*, Ribeirao Preto, Sao Paulo. This group has maintained a strong line of research focused on technological innovations for the treatment of neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, and glioma. Notably, this group aims to conduct research of social interest to support the institutional development of SUS, prioritizing studies for the evaluation and incorporation of new technologies, development of human resources, applicability to the public health system, and development of methods in health services, in compliance with the Federal Decree no. 5895.

Conclusion

The expectations on the use of nanomedicine for the treatment of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and glioma are based on the ability of NPs to traverse the BBB and assist in the administration of therapies, e.g., gene therapy, to the CNS. Added benefits of this technology would include the noninvasive administration and optimized distribution of the drug, reduced side effects, and better therapeutic outcome, all of which could increase the survival rate of patients with brain tumors.

The exchange of information from laboratory research to the clinic is the main challenge for implementing targeted delivery systems because before products are marketed by ANVISA, a long and elaborate process must be completed; this includes three preclinical stages and three clinical trial stages, which may take several years for execution. At present, only few nanotechnological drugs have been approved by ANVISA and are commercially available, including doxorubicin-loaded liposomes for the treatment of ovarian and metastatic breast cancer. In fact, the small number of nanostructured and approved drugs for clinical use is directly related to the lack of specific laws to assess the toxicity of these systems to humans and the environment, thereby demonstrating the urgency for the consolidation of a solid regulation of nanoparticulate drugs. Overall, substantial progress has been made in the field of nanomedicine, and many research groups worldwide are focusing their efforts in the development of effective and safer medical practices that employ nanodelivery systems to treat CNS disorders.

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