

Application of nanodiamond in the diagnosis and treatment of neurological diseases

Qi Zheng *

Shenyang Pharmaceutical University, Shenyang, China

* Corresponding Author Email: zhengqimail@qq.com

Abstract. The blood-brain barrier has long been a barrier to the treatment of neurological diseases in the brain. It protects brain tissues from damage while limiting the access of drugs to the brain for drug delivery, so nanocarriers with smaller particle size are chosen to break the blood-brain barrier. This review summarizes the structural properties of nanodiamond, the interaction mechanism between nanodiamond and blood-brain barrier, and the application of nanodiamond as a carrier in the diagnosis and treatment of neurological diseases, which provides the theoretical basis for the subsequent diagnosis and treatment of neurological diseases.

Keywords: Nanodiamond, Neurodegenerative diseases, Blood-brain barrier.

1. Introduction

How to break the Blood-Brain Barrier (BBB) to deliver drugs to their corresponding locations in the brain with good biocompatibility and targeting efficiency has been a major challenge in the treatment of neurological diseases. In recent years, with the rapid development of nanoscience and technology, there are new options for solving such challenges. Nanodiamonds (NDs) are an emerging class of carbon-based nanomaterials with chemical inertness, good biocompatibility, longer photostability, negligible toxicity, and alternative surface functionalization[1]. Due to these unique physical and chemical properties, NDs have great potential for the diagnosis and treatment of neurological diseases. In this paper, we summarize the interaction mechanism between NDs and BBB from the nature of NDs and their application in the diagnosis and treatment of neurological diseases, which provides the theoretical basis for the subsequent related diagnosis and treatment.

2. Structural properties of NDs

2.1. structural properties of diamond

The prototype of diamond structure is the diamond crystal, also known as diamond. In diamond crystals, each carbon atom forms a covalent bond with four other carbon atoms in sp^3 hybrid orbitals, which are located at 1/4 of the four spatial diagonals, around a carbon atom in the center together to form a positive tetrahedron. Because of the strong C-C bond in diamond, diamond is hard and has an extremely high melting point; and because all valence electrons are confined to the covalent bond region and there are no free electrons, diamond does not conduct electricity[2]. Diamond is stable for all acids. However, it is susceptible to erosion in solutes such as bases, oxygenated salts and metals [3]

2.2. Structure and chemical properties of NDs

NDs retains the structural property characteristics of diamond, it is chemically stable and does not react in hydrofluoric acid, hydrochloric acid, sulfuric acid, or even at very high acid concentrations and extremely high temperatures, and will only be etched in strong oxidizers and at high temperatures for a longer period of time. Also NDs is a diamond micropowder with an average particle size in the nanometer range, which has the dual characteristics of nanoparticles and super hard materials, and has a huge specific surface area (300-400 m^2/g) allowing water molecules to arrange on the surface of NDs forming a dense hydrated layer, improving its stability and ability to bind molecules^{[1][2]}.

Meanwhile, the surface of NDs particles contains a large number of oxygen-containing functional groups such as hydroxyl, carbonyl, and carboxyl groups [3], which enable them to bind to drugs with covalent or non-covalent bonds, modifying them on the surface of NDs and transporting them accurately to target cells and organs to exert their medicinal properties.

3. Structure of BBB and mechanism of action of NDs

3.1. Structure of BBB

The blood-brain barrier is the interface between the central nervous system (CNS) and the peripheral circulation and consists of a cellular gap of approximately 20 nm, which is a barrier between plasma and brain cells and cerebrospinal fluid formed by the walls of brain capillaries and neuroglia and choroid plexus[6], These barriers selectively permeate the solutes in the blood to protect brain tissue from damage by harmful substances in the blood, thus maintaining the internal environment of brain tissue The BBB also limits the ability of the brain to maintain the normal physiological state of the central nervous system. However, the presence of BBB also limits the access of drugs to the brain for administration and the corresponding efficacy. According to a comprehensive medicinal chemistry database, only 5% of the more than 7000 small molecule drugs are used to treat neurocentral system disorders, and these drugs are only used to treat depression, schizophrenia, and epilepsy, with few effective small molecule drugs for most neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease) and brain tumors. Neurological disorders are inherently complex, recurrent, and difficult to diagnose in a timely manner, and the pathogenesis of these disorders is still not fully understood. Therefore, researchers have focused on the design and development of drug-loaded nanoparticles with particle size less than or equal to 200 nm to penetrate the BBB[1], and overcome the limitations of the BBB for the treatment of neurodegenerative diseases.

3.2. Mechanism of action of NDs and BBB

The main mechanisms of NDs-based drug transport through the BBB include receptor-mediated, adsorption-mediated, and cell-mediated endocytosis:

3.2.1. receptor-mediated endocytosis

NDs are modified using receptors on the surface of BBB endothelial cells, and when the modified NDs enter the BBB endothelial cells from the outside, the ligands on the surface of the NDs bind specifically to the receptors on the surface of the endothelial cells and form intracellular vesicles through invagination. These vesicles are then separated from the membrane and transported to the target site to release the drug therein by fusion, degradation, etc.[6]

3.2.2. Adsorption-mediated endocytosis

Techniques for transporting charged nanoparticles or macromolecules to the BBB. Surface modification of NDs with cations to make them positively charged enables electrostatic forces to interact with negatively charged cytoplasmic membranes, enabling binding to the BBB cell surface with low affinity as the process does not involve any specific surface receptor [7]. Thus, adsorption-mediated endocytosis can be delivered using a concentrated form. However, it is important to note that the need for this technique requires surface cation modification of the drug, which may affect its function, and may lead to drug accumulation in other organs due to the non-specific nature of this method[6].

3.2.3. Cell-mediated endocytosis

This technique relies on immune cells (e.g., neutrophils, monocytes, and macrophages) that are able to cross the BBB in both healthy and diseased conditions [8]. In cell-mediated endocytosis, drugs are encapsulated in liposomes so that they can be rapidly absorbed by immune cells in the circulating blood. These immune cells then carry the absorbed drug-laden liposomes across the BBB and use

their permeability and chemotaxis to migrate to sites of inflammation in the brain, allowing the NDs to be taken up by circulating immune cells, which then cross the BBB with the immune cells [6].

4. Application of NDs in diagnosis and treatment

In order to treat the increasing number of patients with neurodegenerative diseases, there is a particular urgency for the development of non-invasive delivery methods, which can alleviate the high costs as well as risk factors of conventional surgery, radiotherapy and chemotherapy[9].

Moscariello et al. prepared human serum proteins modified by cations by encapsulating NDs with DCHSA-based polyethylene glycols. The results showed that fluorescent DCHSA-NDS could reach the brain parenchyma through the BBB and could be traced at the single-cell level[10], enabling a visual and effective tracer technique.

Due to their unique optical, magnetic, and surface degradable properties, NDs also offer a new approach in the detection, diagnosis, and treatment of brain tumors: combining NDs with bionic polydopamine and indocyanine green to form ND PDA-ICG complexes, which use NDs to convert light energy into heat to "burn" tumor cells[11].

It has been shown that there is a significant relationship between neurodegenerative diseases and aging. The biological features of aging include genomic instability, telomere wear, mitochondrial dysfunction, cellular senescence, etc. Neurodegenerative diseases usually exhibit features consistent with aging^[12], and the removal of senescent cells, reversal of aging, and inhibition of SASP may be effective innovative strategies for anti-aging therapy and treatment of neurological diseases. In contrast, NDs, when used as mimetic enzymes, exhibit a variety of activities and can be pH-regulated, as well as possess excellent antioxidant activity, which may help alleviate the aging characteristics of stem cell failure and may also be applied to treat age-related CNS[13][14].

5. Summary

NDs exhibit excellent properties in terms of biocompatibility because of their chemical inertness, non-toxicity, non-luminescence, stability to fluorescence, high sensitivity to surface functionalization, and ability to bind to DNA proteins and other biomarkers as well as drug molecules^[1], making it a highly effective agent that combines diagnostic and therapeutic properties with unlimited potential, not only for breaking the blood-brain barrier with significant It has great potential, not only for breaching the blood-brain barrier, but also for anti-aging and its associated neurological diseases, and has great scope for research and utilization. It can improve the quality and efficiency of many technologies and devices, and we can expect the development of its related technologies to provide better solutions for the treatment of neurological diseases.

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