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Recent Developments of Nanotechnology for Alzheimer's Disease Diagnosis and Therapy

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Abstract

Alzheimer's disease (AD) is a common neurodegenerative disease-causing memory loss and deterioration of cognitive function. In addition, it displays other neurological symptoms such as delusions, deficiency in language, learning, and abstract thinking. The symptoms of the disease progress gradually, which can eventually lead to incapacitation of the individuals functioning. AD will have enormous social and economic impacts in the coming decades. Therefore, strategies for early detection and treatment of AD has become one of the most challenging in modern medicine. Drug and imaging agent's delivery to the brain remains the main problems for the diagnosis and treatment of AD because of the protection of blood-brain barrier (BBB), however, nanoparticles can help overcome the limitations of BBB. In this article, we have explored latest developments in nanotechnology-based AD diagnosis and therapy

Keywords: Alzheimer's disease; Nanoparticles; Nanotechnology; Targeting; Diagnosis; Therapy

Abbreviations: AD: Alzheimer's Disease; BBB: Blood-Brain Barrier; NPs: Nanoparticles; APP: Amyloid Precursor Protein; PS1: Presenilin 1; PS2: Presenilin 2; Aβ: Amyloid-β Protein; CSF: Cerebral Spinal Fluid; MRI: Magnetic Resonance Imaging; SPIONs: Superparamagnetic Iron Oxide Nanoparticles; PEG: Polyethyleneglycol; PLA: Lactic Acid; AuNC: Gold Nanoclusters; AChE: Acetylcholinesterase

Introduction

Generally, nanotechnology refers to the measurement and modeling of substances in a nanoscale manner, which can be applied to engineering and technology by manipulating or modifying material materials to give them new properties. In current medical research, new diagnostic and therapeutic tools were developed combined with nanotechnology, which are beneficial to the specific transport and absorption of drugs and contrast agents to the brain and promote the regeneration of damaged neurons to limit or reverse neurological disorder. New Nano pharmaceutical technology that combines polymer nanoparticles, liposomes, micelles, dendrimers, and nanogels could enhance passage of drugs and small molecules a crossing the BBB.

Pathogenesis

AD as a common neurological disease there were 46.8 million people worldwide living with dementia in 2015 and this number will gradually increase to 131.5 million in 2050 [1]. There were three mutant genes have been reported to cause AD, including the gene encoding the amyloid precursor protein (APP) on chromosome 21, and the gene encoding presenilin 1 (PS1) on chromosome 14 and the gene encoding presenilin 2 (PS2) on the chromosome 1. These mutations can cause the amyloid-β protein (Aβ) to form senile plaques extracellularly, while the microtubule-associated protein tau (Tau) is hyperphosphorylated to form neurofibrillary tangles. These changes throughout the brain leads to extensive cortical damage and early loss of basal forebrain cholinergic neurons [2]. Among them, Aβ has become the main focus of neurodegenerative research and many current treatments are targeted to the production, fibrosis and clearance of Aβ. Although the treatment strategy is advanced, there is no obvious clinical benefit, and currently approved neurotransmitter-modulating drugs can only improve symptoms.

The pathogenesis of AD is multifactorial, and it is not easy to detect behavioral and memory changes caused by disease at an early stage. So, it is important to explore early markers to predict the onset of disease. As a biomarker, current research indicates that Aβ deposition is the first pathogenic event that occurs before clinical symptoms appear, and neurofibrillary tangles promote its development and exhibit detectable clinical symptoms [3,4]. Therefore, it can be speculated that Aβ and Tau proteins have been concentrated in cerebral spinal fluid (CSF) before clinical onset. In addition to exploring biomarkers,

because the net charge of Aβ is negative, multivalent cations can bind Aβ and accelerate the process of aggregation and fibrillation, thus monitoring plasma multivalent cations (eg zinc, copper, iron, etc.) are expected in the early detection of AD [5].

Nanotechnology in the Diagnosis of AD

Since neuro invasiveness and degenerative changes have begun before the onset of AD symptoms, early diagnosis is the key to effective treatment of AD. Most studies focus on magnetic resonance imaging (MRI) using contrast-doped NPs or labeling NPs with fluorescent probes to detect and identify amyloid plaques.

Iron oxide NPs

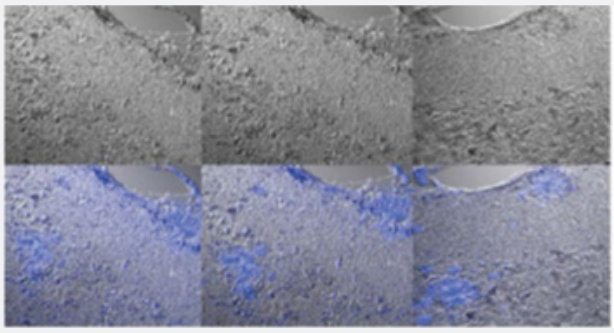

Figure 1: Histochemical stained Aβ plaques on serial brain sections of Tg2576 mice.

Magnetic iron oxide NPs have gained wide attention due to their large surface area, good magnetic properties, low toxicity, and good biocompatibility and degradability. For example, Cheng et al. [6] synthesized superparamagnetic iron oxide nanoparticles (SPIONs) connected with curcumin which coated with polyethyleneglycol (PEG)-lactic acid (PLA). The material is non-cytotoxic and has the ability to detect amyloid plaques in the brain of Tg2576 mice with AD [7] (Figure 1). Both top and bottom images were viewed by confocal microscopy. Top images were bright view and bottom images were fluorescence signal from stained chemical (from left to right stain by thioflavin T, curcumin or curcumin-MNPs) [7].

Gold NPs

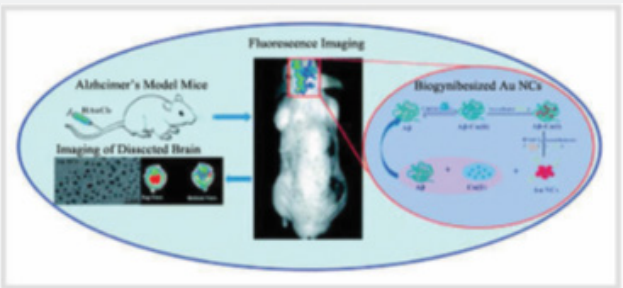

Figure 2: This diagram showed that intravenous injection of aqueous HAuCl4 through the AD mice tails showed exact bright fluorescence labeling around the affected sites of the Alzheimer's brain [8].

Lai et al exposed these sites to an aqueous solution of chloroauric acid to form a gold salt by targeting the site of infection [8]. These salts are assembled into gold nanoclusters (AuNC) for fluorescence imaging. Within a few hours after the injection of chloroauric acid by the tail vein of AD mice, there was a clear fluorescent label around the affected part of the brain, whereas the control mice did not show any fluorescent area after intravenous injection of chloroauric acid for 24 hr (Figure 2).

Nanotechnology in the Treatment of AD

BBB is the primary barrier to the delivery of therapeutic drugs to the brain. Some treatments have forced them to open by causing structural damage to the BBB, at which point the BBB has lost its selectivity for drug passage. The carrier system combined with nanotechnology is the most promising treatment strategy for delivering drugs to the brain through the BBB. The current common delivery systems are shown in (Table 1) [9].

Table 1: Several commonly used nanocarrier systems.

Nanocarrier Systems	Structure	Effect
Liposomes	Small vesicles composed of single or multi-layered bilayer lipids surrounding a central aqueous chamber	Targeted delivery therapy; prolonged circulation time in the body; sustained release
Micellar	Hydrophobic core and hydrophilic polymer shell	The core is incorporated with a lipophilic compound; the shell is used to stabilize the micelles and hide the drug
Nanogel	Composed of ionic and nonionic polymer chains	High load capacity and stability; Respond to ionic strength, temperature, pH, etc.; Reduce drug absorption in liver and spleen
Dendritic macromolecule	Polymer formed by crosslinking of repeating monomer units	Internal nanostructures can embed several therapeutic agents; external groups can be combined with ligand

Cholinergic anti-inflammatory effects play an important role in preventing the development of learning and memory disorders in AD patients, so acetylcholinesterase (AChE) inhibitors can be used for symptomatic treatment of AD. As an inhibitor of AchE and butyrylcholinesterase, rivastigmine was approved by the FDA in 2000 for the treatment of AD. Studies have shown that coating the drug in nanoparticles enhances the targeted delivery of rivastigmine and reduces the side effects of free drug administration [10-13].

Curcumin can enhance mitochondrial function and may be suitable for preventing AD. However, the bioavailability of curcumin is low. Some studies have suggested that the bioavailability of curcumin micelles is higher than that of natural

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curcumin, and the encapsulation of nanoparticles can increase the solubility of curcumin, prolong the circulation time in the body, and improve the Targeted release within brain [14-17]. There is also evidence that metals have the effect of damaging neurons. The level of metal ions can be reduced by the use of chelating agents that target the interaction between Aβ and metal ions in the brain of AD patients [18,19].

Limitations of Combining Nanotechnology to Treat AD

It is well known that NPs will be immediately covered by proteins to form protein crowns after coming into the biological environment [20], and the effect of protein crowns on Aβ fibrosis should be assessed. Different diseases may also alter the fate of NPs in the body, so NPs may also have different therapeutic effects or toxic effects after entering different patients. These studies suggest that in the future research of Nanotechnology, a variety of hidden factors in the nanobio interface should be considered. The potential toxicity of NPs is another important issue, and there are few reports around long-term toxicity after NPs use. In order to solve these problems, it has been expected to develop multifunctional NPs with multiple therapeutic capabilities, for example, comprehensive control of Tau protein phosphorylation, inflammatory response, redox reaction and improvement of mitochondrial.

Research undertaken so far to transport drugs via nanocarriers across the BBB, while considerable, has certainly not enough and has not met expectations [21], so there is an urgent need to re-examine current research ideas and methods to improve or find new ways.

Conclusions and Future Prospects

Since the discovery of central nervous system degenerative diseases, its diagnosis and treatment have become a huge medical challenge. In addition to research in the biological field, the combination with other fields, especially the integration of nanotechnology, has showed us a promising way. Current research indicates that the surface of NPs can be modified by covalent and non-covalent connection, giving it additional stability and drug affinity. In the future, we hope to see nanotechnology-based drug delivery systems can effectively treat more Invasive neurological disease or drug resistant disease. In addition, the functionalization of NPs and the combination of drugs indicate more possibilities, not only for drug system construction, but also for gene and protein delivery. Some nanoparticles also have special magnetic and optical properties, etc., giving them magnetic targeting and photothermal effects. With the advancement of nanotechnology, NPs will appear more in biomedical application.

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