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The long and the short of current nanomedicines for treating Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disorder with complex pathological mechanisms and an increasing incidence year by year,[1] and the main manifestations of AD patients are memory loss and cognitive dysfunction. Several drugs currently approved by the US Food and Drug Administration (FDA) can only improve the symptoms of patients with AD, but cannot delay the progression of the disease or completely cure the disease.[2] In recent years, drugs screened for targeting AD pathology have shown good positive results in cell and animal models, but most of them have failed in clinical trials.[3] In recent years, nanomedicine has developed rapidly, and nanotherapeutics can play a role in helping drugs to cross the blood–brain barrier (BBB) and for targeted delivery and controlled release, providing a new treatment scheme for AD.[2,4]

THE PATHOLOGICAL MECHANISM OF AD AND CURRENT STATUS OF TREATMENT

Despite decades of basic and clinical research, the pathological mechanism of the disease is not fully understood so far. At present, hundreds of hypotheses about the pathological mechanism of AD have been proposed, among which the mainstream hypotheses include the amyloid cascade hypothesis, the tau hyperphosphorylation hypothesis, the oxidative stress hypothesis, the cholinergic hypothesis, and so on.[1] The BBB can prevent almost all macromolecular drugs and most micromolecular drugs from entering the brain by acting as a physiological parclose of the central nervous system (CNS).[5] While it plays an important protective role, it also poses great challenges for the treatment of cerebral illnesses such as AD. At present, the drugs approved by the FDA for the treatment of AD generally have some problems, such as large adverse reactions, low effective concentration in the brain, and poor therapeutic effects.[2] Although many candidates for various therapeutic targets had been continuously screened out and these candidate drugs had gained positive results in preclinical research, they failed to show the ideal effect in clinical trials. The main reasons for treatment failure were low bioavailability due to the first-pass effect, low effective intracranial concentration due to poor targeting ability, severe side effects due to high dose requirements, and others. With the application and development of nanotechnology in medicine, therapeutic drugs can use nanomaterials as carriers to efficiently penetrate BBB and deliver the drug targeted to the lesion site, which brings new hope for the treatment of AD.

NANOMEDICINE FOR THE TREATMENT OF AD

The difficulty in the treatment of neurodegenerative diseases is how to overcome the limitation of the BBB to

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deliver drugs to the CNS. Nanoparticles (NPs) used to treat AD are typically particles less than 100 nm in size and capable of penetrating biological barriers (such as BBB).[1] They can be used as carriers to deliver therapeutic drugs to specific sites, thus overcoming the shortcomings of traditional therapies and achieving good therapeutic outcomes. Nanomaterials could be used to deliver hydrophilic or hydrophobic drugs to the brain because they are usually amphiphilic. In addition to being biodegradable, biocompatible, and nontoxic, the ideal nanomaterials selected as Nano capsules also need to have an appropriate particle size, zeta potential, and lipid solubility.[1] Among various nanomaterials, drug delivery systems that have currently been investigated for the treatment of neurological diseases (especially AD) include organic NPs (such as polymeric NPs, lipid-based NPs, carbon nanotubes) and inorganic NPs (such as magnetic NPs, quantum dots, and metal NPs).[6] Nano-drug delivery system (NDDS) is a kind of carrier for targeted therapy by penetrating BBB with auxiliary drug molecules and delivering and releasing drugs to the lesion site to improve the bioavailability of drugs. At present, some nano-composite drugs loaded with drug molecules for treating AD have shown encouraging results in animal models, and this drug delivery system is emerging as a promising strategy for treating AD.[7]

ADVANTAGES OF NANO-DRUG THERAPY FOR AD

In the treatment of neurological diseases, especially AD, compared with conventional drugs, nano-drugs have obvious advantages in many aspects. They (1) provide a good carrier platform for transporting therapeutic drugs in the blood and penetrating the BBB into the CNS; (2) improve the biocompatibility of therapeutic drugs, and the nano-carrier itself has biocompatibility and biodegradation; (3) improve the stability of therapeutic drugs in the blood and tissues to avoid premature degradation by enzymes; (4) improve the pharmacokinetics and pharmacokinetic indexes, and prolong the half-life time and action time through continuous drug release; and (5) effectively reduce drug dosage, drug frequency, and the incidence of side effects.[2,8]

DIFFICULTIES AND CHALLENGES

Although nano-drugs for AD have shown positive results in cell and animal studies, clinical applications are still a long way off. This is due to the following reasons. First, these experimental models are too simplistic and ignore that AD is an intractable neurodegenerative disorder influenced by multiple pathogenic factors.[1] Second, the results of nano-drugs *in vitro* and *in vivo* are usually different. The reason is that nano-drugs are easy to adsorb various protein molecules on their surface and form "protein corona" after entering a more complex *in vivo* environment.[6] This protein coating can affect the physical and chemical properties of the NPs (such as particle size and zeta potential), thus changing their stability, membrane permeability, and drug delivery ability, and even exacerbating their biological toxicity. It remains to be solved how nano-drugs can perform drug delivery functions by specifically and efficiently targeting CNS without interacting with other molecules and cells after entering the blood. In addition, when nano-drugs are injected into the body, they may activate an autoimmune response; as nano-drugs may be toxic to some extent, the current low targeting efficiency requires increasing the dose of nano-drugs to improve the curative effect, which will further magnify the toxicity.[1] Because of the need for the treatment of AD, long-term repeated injection of nanomaterials will inevitably lead to the accumulation of nanomaterials in the body without timely and effective degradation, especially in the brain tissue, which will lead to brain damage.[9] Therefore, the necessary safety assessment of nanomedicine should be conducted before clinical trials. What is more, long-term repeated use of nano-drugs may also lead to resistance problems; the stimulative effect of nanomedicine on the CNS may cause the problem of addiction.[5] In addition, the cost of synthesizing nanomaterials is also an issue that cannot be ignored. At present, the synthesis technology is not mature, and the production of nanomaterials is a complex synthesis process with more input than output. The cost of nanomedicine therapy is a serious constraint to the routine treatment of AD.[10] These problems severely limit the usefulness of nano-drugs in clinical treatment.

FUTURE DEVELOPMENT PROSPECTS

Although AD is a kind of refractory neurodegenerative disease, the development of nanomedicine has brought new therapeutic ideas to the treatment of AD. Although the therapeutic effect of most NDDSs is not ideal and there are still many problems that need to be solved (such as poor central targeting ability, low bioavailability, and severe toxicity),[5] nanomedicine with multiple advantages is still regarded as one of the most promising treatment methods for AD. It is an important research direction of nanomedicine to design and select nanocapsule materials with high efficiency of targeted therapy, good biocompatibility, and low toxic side effects. The importance of improving the targeting performance of nanomaterials lies in facilitating nanomaterials to accurately deliver a certain dose of therapeutic drugs to pathological tissues or cells efficiently, to improve the efficacy and reduce the drug dose and toxic side effects. Surfactants or hydrophilic

materials such as polyethylene glycol (PEG) can be added to the surface of NPs to improve the characterization, structure, performance, and targeted delivery performance of the nanocarrier, thus improving the therapeutic effect in AD.[6,11] In addition, as the pathogenesis of AD is complex, there may be multiple pathogenic factors acting independently or synergistically. Therefore, the design of nanocarriers that can simultaneously load and deliver different therapeutic drugs to multiple therapeutic targets (phosphorylated tau protein, amyloid β protein, mitochondrial dysfunction, neuroinflammation, *etc.*) will significantly and effectively improve the therapeutic efficacy of the drugs in AD and overcome the disadvantage that current drugs can only target a single therapeutic target and fail to achieve satisfactory efficacy.[12] At present, in addition to loading therapeutic drugs, nanocarriers can load nucleic acids for gene therapy of AD.[13] The combination of stem cell therapy and nanotechnology in the treatment of AD is also a hot research trend.[10] The new technology works by using nanotechnology to promote tissue regeneration and repair or stimulate and regulate the proliferation and differentiation of stem cells.[10,14] With the continuous development of nano-medical technology, it will be possible to successfully overcome the problems encountered in treating AD in the future.

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Conflict of Interest

The authors declare to have no competing interests.

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