

Hydrogel: A promising new technique for treating Alzheimer's disease

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INTRODUCTION

Alzheimer's disease (AD) is a neuro-degenerative disease that seriously affects human health. Currently, there are only five drugs approved by the Food and Drug Administration (FDA) for the treatment of AD (donepezil, galantamine, rivastigmine, tacrine, and memantine).^[1] These drugs can only improve the symptoms of AD patients, but cannot delay or reverse the progression of the disease.^[1] Among them, tacrine is delisted because of more serious side effects. Aducanumab, the only recently approved drug currently expected as a potential treatment for AD,^[2] remains controversial. Therefore, research and development of effective drugs for the treatment of AD has become a hotspot of current AD research.

APPLICATION OF HYDROGEL IN THE TREATMENT OF AD

Characteristics of hydrogel

Hydrogel is a kind of three-dimensional network gel with an extremely high hydrophilic structure. After receiving physical (such as temperature), chemical, or biological stimulation signals, various polymer monomers gelate and form hydrogel in the presence of a crosslinker.^[3,4] In recent years, hydrogels have been widely used in the treatment of various diseases due to their performance advantages such as good controlled drug release, degradability, biocompatibility, and stable mechanical

strength.^[5,6] Hydrogels can continuously and slowly release therapeutic drugs in the body, including chemical drugs, protein drugs (such as neurotrophic factors), and stem cells,^[3,7,8] which can achieve long-term treatment of diseases.

Application of hydrogel in the treatment of AD

Hydrogels have also attracted much attention in the treatment of neurodegenerative diseases such as AD.^[5,6] Hydrogel administration methods include intranasal administration, microneedle patch, subcutaneous injection, or intracranial injection.^[9–12] At present, intranasal administration is mostly used in the treatment of AD by hydrogel technology. Intranasal administration is a new method of administration, which can make drugs bypass the blood–brain barrier (BBB) and reach the brain quickly through the cerebral nerve (trigeminal nerve or olfactory nerve) pathway.^[13,14] For example, the nasal situ hydrogels of timosaponin BII showed a good therapeutic effect on AD^[15] and good pharmacokinetic results were obtained by intranasal administration of donepezil-loaded hydrogel.^[16] Sustained release of donepezil can be achieved safely and effectively through subcutaneous injection of donepezil hydrogel preparation, thus reducing the frequency of administration for AD patients.^[11] Donepezil hydrogel microneedle patch can produce a relatively high and stable blood concentration in animal models.^[10] In addition, the use of hydrogels slow-release drug performance and nanometer carrier through BBB and

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Access this article online

Website:

www.intern-med.com

DOI:

10.2478/jtim-2022-0008

cell membrane characteristics, the injectable biodegradable hydrogels load specific nanoparticles (*i.e.*, nanocomposite gels), may be able to achieve better effect of continuous targeted delivery.^[17,18] Also, using nanocomposite gel to deliver stem cells and neurotrophic factors can achieve a more ideal anti-AD effect.^[17,18]

The advantages of hydrogel in the treatment of neurodegenerative diseases such as AD include the following: (1) hydrogel is injected locally, which can effectively overcome the toxic side effects and off-target effects caused by large doses of systemic administration;^[3,19] (2) it avoids the injuries caused by surgical treatment or direct injection of drugs into the brain tissues;^[9] (3) compared with surgical treatment, the hydrogel can effectively reduce tissue damage and also reduce the pain and economic burden of patients; (4) in addition to hydrogel sustained-release drug, can also protect the stem cells from the surrounding tissue on the spatial structure of the mechanical compression, effectively prevent immune cells for transplantation of stem cells in the immune attack, reduce the body's immune response, make the normal stem cells play a role of treatment of regeneration and secrete neurotrophic factors (such as multidirectional differentiation, *etc.*);^[20] (5) in addition to therapeutic drugs, targeted delivery of neurotrophic drugs (factors) to the lesion site can effectively repair the nerve cells or affect the vitality and function of nerve cells, which also has great therapeutic significance in neurodegenerative diseases.^[21] Therefore, the hydrogel has obvious advantages in the treatment of AD and broad developmental prospects.

Problems in the treatment of AD with hydrogel

Although hydrogel has obvious advantages in treatment of AD, research on hydrogel in treating AD still faces a lot of problems. (1) First of all, the range of drugs that hydrogels can load is limited; in the present study, the use of hydrogel-encapsulated drugs mostly focused on symptom-improving drugs such as donepezil^[10,16] and therapeutic drugs for A β pathology.^[22] (2) Secondly, as an exogenous synthetic or natural substance, the biocompatibility and biodegradability of hydrogel materials must be considered before they are applied into clinical practice.^[9,17,18] Whether hydrogels and their degradation products will cause immune or inflammatory reactions in human tissues or organs (such as the brain) and whether long-term drug use will accumulate in the body and produce toxicity are the problems worthy of in-depth study.

VISION FOR THE FUTURE

Due to its advantages of sustained drug release, reduction of systemic toxic and side effects, and avoidance of surgical

injury, the hydrogel drug delivery system has been well applied in preclinical studies of AD,^[9] especially hydrogel loaded with stem cells,^[17] which is expected to help break through the dilemma of AD treatment. However, the toxicity and safety of hydrogel material on the human body are still worthy of attention. Although the application of hydrogel in the treatment of AD is still in its infancy, with the continuous development of new hydrogel materials with high biocompatibility and new AD drugs, the hydrogel drug delivery system is bound to be an exceedingly promising therapy method for AD.

Source of Funding

This work was supported by the National Natural Science Foundation of China (No. 81771964 and 82072051), Shanghai Natural Science Foundation (#22ZR147750), Science and Technology Support Projects in Biomedicine Field of Shanghai Science and Technology Commission (#19441907500), innovative clinical research project of Changzheng Hospital (2020YLCYJ-Y02), and Characteristic Services of Veteran Cadres Memory Disorders Diagnosis and Treatment in Changzheng hospital (2020CZWJFW12).

Conflict of Interest

The authors declare to have no competing interests.

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How to cite this article: Gong B, Cheng W, Ji W, Chen X, Chu J, Liang W, *et al.* Hydrogel: A promising new technique for treating Alzheimer's disease. *J Transl Intern Med* 2022; 10: 188-190.