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PROGRESS AND FUTURE OF HYDROGELS IN THE TREATMENT OF CENTRAL NERVOUS SYSTEM INJURIES

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Abstract

Hydrogels have become essential biomaterials in the treatment of central nervous system (CNS) injuries due to their unique properties, which include biocompatibility, bioresorbability, and the ability to mimic the natural extracellular matrix. These materials are used in a variety of applications, such as neural regeneration, controlled drug release, and support for cell therapies. Injectable hydrogels, due to their adaptability, allow localized administration in the affected areas, creating a favorable environment for the proliferation and differentiation of nerve cells. Recent technological advances, such as the integration of nanotechnology and the development of stimulable hydrogels, have significantly expanded their therapeutic potential. Smart hydrogels can respond to specific stimuli, adjusting their properties or releasing bioactive agents in a controlled manner. Also, 3D bioprinting allows the creation of custom structures, replicating the architecture of damaged tissues, while artificial intelligence facilitates the optimized design of hydrogels. This review explores current applications and recent advances of hydrogels in the treatment of CNS, highlighting their impact on neuronal regeneration and prospects for the development of advanced therapeutic solutions. Hydrogels promise to become an essential component in neuroregeneration and neurosurgery, helping to transform treatments in these areas.

Keywords*:* Hydrogels, neuroregeneration, CNS, biocompatibility, controlled release, nanotechnology, 3D bioprinting.

Introduction

Central nervous system (CNS) injuries are a major public health problem, having a significant impact on the quality of life of patients. Due to the complexity of the CNS and its limited capacity for regeneration, conventional treatments are often insufficient for the complete restoration of lost neuronal functions. Advances in biomaterials engineering have opened up new opportunities in the treatment of CNS injuries, and hydrogels have stood out as promising solutions due to their unique properties [1,2].

Hydrogels are three-dimensional polymeric materials capable of absorbing large amounts of water, thus mimicking the natural extracellular matrix of biological tissues. This hydrated structure gives them biomechanical and biochemical properties suitable for CNS uses, such as supporting neuronal growth and differentiation, controlled release of growth factors, and regeneration of affected tissues. Moreover, their ability to be customized through chemical

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functionalization or integration of nanoparticles makes them ideal for advanced therapeutic applications [1-4].

In addition to their physicochemical advantages, hydrogels are compatible with various therapeutic strategies, including cell therapies, localized drug delivery, and use in combination with 3D bioprinting techniques. For example, injectable hydrogels have demonstrated remarkable potential in nerve tissue repair due to their ability to adapt to the shape of the lesion and create an environment conducive to neuronal regeneration [1-5].

However, the use of hydrogels in the CNS is not without its challenges. Stability in the biological environment, the risk of immunogenicity, and the difficulties of clinical integration are critical aspects that need solutions. However, recent research has taken important steps in overcoming these limitations, starting with the development of smart hydrogels, capable of responding to specific stimuli, and up to the integration of these materials with advanced technologies, such as nanotechnology or artificial intelligence [2-5].

The purpose of this review is to analyze recent progress in the use of hydrogels for the treatment of CNS injuries, highlighting their relevant properties, current applications, challenges, and prospects. By exploring these aspects, we aim to outline a comprehensive framework on the role of hydrogels in neuroregeneration and neurosurgery, contributing to the understanding of their importance for the development of innovative therapeutic solutions. Thus, this review combines fundamental aspects with recent discoveries to provide a clear vision of the potential of hydrogels in transforming treatments in neurology and neurosurgery.

Properties of CNS-relevant hydrogels

Hydrogels are unique biomaterials, characterized by a three-dimensional structure capable of absorbing large amounts of water, similar to the natural extracellular matrix of biological tissues. This hydration capacity gives hydrogels essential biomechanical and biochemical properties for their use in the central nervous system (CNS) [3-6].

A crucial aspect of hydrogels is their high biocompatibility, which allows them to be integrated into biological tissues without causing significant inflammatory reactions. They can also be bioresorbable, degrading over time in a controlled manner, making them ideal for temporary or regenerative support applications [3-7].

Hydrogels can be chemically functionalized to include growth factors, proteins, or nanoparticles, thus facilitating the controlled release of these therapeutic agents directly to the affected area. The adjustable elasticity and viscosity of hydrogels allow them to be adapted to different types of lesions and clinical conditions [4-7].

In addition, these materials provide a favorable environment for cell proliferation and neuronal regeneration, stimulating interactions between cells and supporting axonal reconnection. These properties make hydrogels a promising tool for the treatment of CNS lesions and neuroregeneration [4-8].

The table summarizes various types of hydrogels, their sources, and key properties relevant to brain tissue regeneration, including immunogenicity, biodegradability, porosity, biocompatibility, and their ability to support neuronal and axonal growth. Natural hydrogels exhibit high biocompatibility, while synthetic ones allow greater customization for specific needs (table 1.) [4-9].

Table 1. Summary of hydrogel types and properties for neural applications [4-10].

Hydrogel type	Source	Immunogenicity	Degradability	Porosity	Biocompatibility	Neuronal support	Axonal growth
Hyaluronic acid (HA)	natural	low	high	high	excellent	promotes	facilitates
Collagen type I	natural	moderate	moderate	high	excellent	supports	facilitates
Alginate	natural	minimal	poor	low	good	limited	limited
Chitosan	natural	minimal	moderate	moderate	excellent	supports	limited
Methylcellulose	natural	minimal	moderate	high	excellent	promotes	facilitates
Fibrin	natural	moderate	moderate	moderate	high	promotes	supports
Gellan gum	natural	moderate	moderate	high	moderate	limited	limited
Self-assembling peptides	semi-natural	moderate	variable	high	excellent	promotes	facilitates
Polyethylene glycol (PEG)	synthetic	low	minimal	variable	moderate	limited	limited
Methacrylate (MA)	synthetic	minimal	high	high	excellent	supports	promotes

Current applications and recent technological advances of hydrogels in the treatment of CNS

Hydrogels have gained considerable interest in the treatment of central nervous system (CNS) injuries due to their unique properties, which allow them to be used in a variety of therapeutic applications. These materials provide essential support for the regeneration of neuronal tissues, helping to restore lost functions. In addition, recent technological advances have further expanded the potential of hydrogels, paving the way for more effective and personalized therapies [8-13].

Hydrogels are widely used as a support for the regeneration of damaged tissues. Due to their three-dimensional structure, they can mimic the natural extracellular matrix, creating a favorable environment for nerve cell proliferation and differentiation. Injectable hydrogels are particularly valuable because they can be administered directly to the affected area, adapting to the shape and size of the lesion. They are successfully used to repair traumatic spinal cord injuries, strokes, and other degenerative conditions [9-13].

Another important area of application is the controlled release of drugs and growth factors. Hydrogels can be chemically functionalized to include bioactive molecules that are gradually released into the affected area, thus reducing the need for repeated administration and minimizing systemic side effects. This strategy is used to stimulate axonal regeneration, reduce inflammation, and prevent glial scarring [9-14].

Hydrogels are also used as a support for cell therapies, including stem cell transplantation. They provide a protective environment for the transplanted cells, increasing the chances of survival and integration into the host tissue. In combination with gene therapies, hydrogels can accelerate neuronal regeneration and restore lost functions [10-15].

In recent years, the development of hydrogels has made significant progress thanks to the integration of advanced technologies. A notable example is the use of nanotechnology to functionalize hydrogels. The nanoparticles included in the structure of hydrogels can amplify therapeutic efficiency by acting as transport systems for drugs, proteins, or DNA. These nanoparticles can be designed to respond to specific stimuli, such as pH or temperature variations, releasing therapeutic agents exactly when and where they are needed [11-16].

Stimulable hydrogels, also known as smart hydrogels, are another important advance. They can respond to physical (temperature, light), chemical (pH, ionic concentration), or biological (enzymes) stimuli, adjusting their properties or releasing therapeutic agents in a controlled manner. Thus, stimulable hydrogels allow greater adaptability to complex CNS conditions, improving the efficiency of treatments [9,11-17].

3D bioprinting has also revolutionized the use of hydrogels in neuroregeneration. This technology allows for the creation of custom structures, which can be designed to replicate the specific architecture of damaged neural tissue. Hydrogels used in bioprinting can be loaded with stem cells or other bioactive components, providing precise support for regeneration [14-18].

Another promising area is the integration of artificial intelligence into the design of hydrogels. Through the analysis of complex data, AI can help identify the optimal combinations of polymers and biofactors for the development of customized hydrogels tailored to the individual needs of patients [15-19].

The integration of current applications with recent technological advancements provides advanced solutions for the treatment of CNS injuries. For example, injectable hydrogels combined with smart nanoparticles can provide both physical support for regeneration and controlled drug release, maximizing therapeutic effectiveness. At the same time, the use of 3D bioprinting for the creation of custom structures brings a high level of precision and adaptability [7,15-20].

These advances create the premises for more effective therapies while reducing the risks associated with conventional treatments. In the future, hydrogels are expected to become an essential component in personalized treatments, transforming the way we approach CNS regeneration and rehabilitation [16-23].

Conclusions

Hydrogels represent an innovative and promising solution for the treatment of central nervous system (CNS) injuries, offering a unique combination of biocompatibility, personalization, and functionality. Due to their ability to mimic the extracellular matrix and support neuronal regeneration, these biomaterials have become a central pillar in advanced therapies for neurological conditions.

Current applications of hydrogels include tissue regeneration, controlled drug release, and cell therapy support, all of which contribute to improved clinical outcomes. Injectable hydrogels, in particular, allow adaptability to complex lesions, creating a favorable environment for cell proliferation and differentiation. In addition, integration with nanotechnology and the development of smart hydrogels have significantly expanded their applicability, facilitating the targeted release of bioactive agents and adaptive responses to specific stimuli.

Recent technological advances, such as 3D bioprinting and the use of artificial intelligence, have strengthened the therapeutic potential of hydrogels. 3D bioprinting allows the design of custom structures that replicate the architecture of neural tissues, providing precise support for regeneration. In parallel, artificial intelligence helps to optimize the combinations of polymers and biofactors, contributing to the development of customized solutions for the specific needs of patients.

However, there are also significant challenges that need to be overcome to ensure large-scale clinical integration of hydrogels. These include long-term stability in the biological environment, immunogenicity risks, and the complexity of the industrial-scale production process. However, ongoing research focuses on addressing these issues, and recent progress offers optimistic prospects.

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