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Review Article

Injectable Hydrogels in Repairing Central Nervous System Injuries

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The injured central nervous system (CNS) can hardly regenerate. In vitro engineering of brain tissue hits technical bottlenecks. Also, the compaction and complexity of anatomical structure defy the accurate positioning for lesion sites in intracranial injuries. Therefore, repairing injured CNS remains a significant clinical challenge. Various recent in vivo and in vitro experiments have demonstrated the excellent effect of tissue engineering on repairing central nerve cells and tissues through implanting new materials and engineered cells. Except for porous three-dimensional structures able to pad lesions in various shapes and simulate the natural extracellular matrix with nutrients for cell proliferation, hydrogels incorporate high biocompatibility. Injectable hydrogels with the merits of avoiding complex surgery on large wounds, filling irregular gaps, delivering drugs, and others, are of growing interest. This review focuses on the experimental studies regarding injectable hydrogels, especially applying various injectable hydrogels to repair brain damage.

1. Introduction

The CNS consists of the brain and the spinal cord, constituting the most complex part of the nervous system; the brain works as the "commander" to integrate and regulate all information of the nervous system [1, 2]. Injuries to the CNS caused by traumatic brain injury (TBI), neurodegenerative diseases, neurodevelopmental disorders, stroke, brain tumors, and other diseases may lead to disorders in movement, sense, cognition, and deglutition [3–5]. Astrocytes rapidly migrate to the injury site to prevent further damage to the neural network, forming glial scars around the injury site. The poor regeneration of neurons and axons in the CNS and glial scar formation at the lesion make brain damage irreversible, resulting in long-term disability [6]. Clinical attempts to repair adult CNS injuries include cell transplantation and inhibitory antibodies [7]. For example, neural stem cell transplantation could promote injury recovery by facilitating axons and neurons regeneration. However, no physical support to fill the lesion and provide a microenvironment for cell growth and differentiation make neural stem cell transplantation inadequate for extensive brain injury [8, 9]. Therefore, the application of biomaterials scaffold to fill the brain lesion has emerged into focus.

The application of biomaterial scaffolds to tissue regeneration has long been established, such as the regeneration of soft tissue, bone, and peripheral nervous system, with favorable effects [10, 11]. Implementing the application of biomaterials to brain injury regeneration requires fulfilling certain conditions. For example, the biomaterials shall incorporate the mechanical properties similar to brain tissue, the capacity to deliver nutrients or cells, moderate degradability, biocompatibility, anti-inflammation, and others [12, 13]. Hydrogels proved to be an ideal biomaterial for brain tissue regeneration. Except for three-dimensional (3D) crosslinked polymer networks with water content over 90%, hydrogels incorporate adjustable physical and chemical properties to fill the irregular pathological cavity in the brain, providing a favorable microenvironment for nerve cells growth and proliferation [14].

Moreover, the porous interior structure makes hydrogels soft and flexible to minimize tissue damage [15]. Traditionally, the hydrogels applied to repair CNS injuries are noninjectable and highly viscous. Such hydrogels are often diverted into implantable biomaterial scaffolds or external wounds dressings in tissue engineering [16]. Noninjectable hydrogels used in the regeneration of brain injury require mechanical properties similar to those of brain tissue, and common types include poly hydrogels based on polyethylene glycol (PEG) or poly 2-hydroxyethyl methacrylate (poly-HEMA). The cell adhesion of hydrogels improved significantly after modification with RGD sequence and natural materials such as agarose, alginate, gelatin, HA, and chitosan, which enhanced the application effect of noninjectable hydrogels as biomaterial scaffolds on repairing brain injuries [17]. However, the physical properties of noninjectable hydrogels require extensive surgical incisions for application, or only implantation in open surgeries (Figure 1), limiting their application scope [19]. Besides, implanted biomaterials often elicit neuroimmune responses. The implantation will break the blood-brain barrier, and plasma and peripheral blood cells will enter the ventricle. The influx of fluid and peripheral blood cells, including macrophages and lymphocytes, can trigger inflammation and elicit neuroimmune responses [20]. Injectable hydrogels can deliver drugs or cells to the injured site of the brain directly, saving the blood-brain barrier from damage. Injectable hydrogels can be used both as a drug delivery platform for the CNS and scaffolds for transporting neural stem cells [21]. Redesigning the physical and chemical properties could speed up the gelation of injectable hydrogels after injection, which causes clearance of cerebrospinal fluid and limits wide spread to maintain local release of hydrogel in the lesion area [22, 23]. The use of injectable hydrogels adapts to the brain environment with the ongoing development of minimally invasive surgery and meets the new requirements of biomaterials for smaller surgical sites. This review introduces the physical and chemical properties and advantages and disadvantages of injectable hydrogels composed of different components and discusses the application of these hydrogels in repairing brain nerve injuries caused by diseases and the development prospect of injectable hydrogels in repairing brain injuries.

2. Biomaterials for Repairing Brain Injuries

Biomaterials are emerging in the study of brain tissue engineering. Distinct from other organs, the brain is complex in structure and function. The site of brain damage is sometimes deep and sometimes covering functional tissues. The biomaterials used to repair brain damage should be biocompatible with the brain tissue and able to prevent the other functions of brain tissue from interference. Therefore, the biomaterial properties regarding tissue engineering in repairing brain injuries are significant.

2.1. Intracranial Delivery. The implantation of biomaterials should not cause damaging pressure on the host brain tissue and avert irreversible damage to tissue function [24].

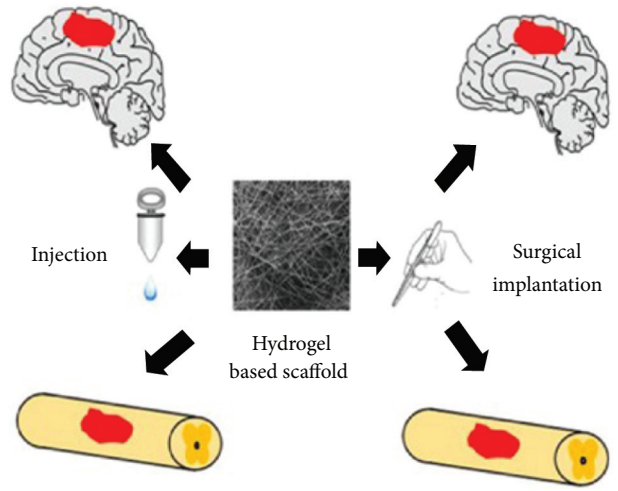

Figure 1: Application of injectable hydrogel and noninjectable hydrogel in regeneration of central nervous system [18] (Copyright © 2018 Yanchao Wang et al.).

Moreover, biomaterials require adapting to and filling the different pathological cavities with various topological structures and guaranteeing good interaction with the brain tissue. Ideally, the implanted biomaterial can facilitate the penetrability, proliferation, and differentiation of the implanted cells to some extent [25, 26]. For the time being, most injectable hydrogels can provide such geometrical configuration [27]. Besides, the delivery of hydrogels in a fluid state into the cranial cavity through tiny diameter needles or catheters causes shear stress. Differences in internal diameters between liquid storage vessels, conduits, and needles can cause various shear stresses and pressures on the fluid material in each interval, affecting material properties [22, 28]. Also, excessive injection pressure causes additional tissue damage. However, the materials released to the damaged site after shear force and pressure need time-dependent self-repairing to restore the viscous fluidity. Injectable hydrogels injected into the intracranial cavity in a fluid state need a suitable rate to gelatinize. Short gelation will clog needles and catheters [29, 30]. Long gelation may cause the diffusion or even loss of implantable cells and drugs and fail to provide adequate structural support for the diseased cavity [31].

2.2. Mechanical/Rheological Properties and Aperture Size. Biomaterials used in tissue regeneration should incorporate mechanical properties that match those of host tissues. Some studies exhibit stronger differentiation of neural progenitor cells on scaffolds of similar mechanical strength to the brain [32] (Table 1). Besides, cell invasion and migration vary with the material hardness. Softer tissues allow faster cell migration. Cells show stronger invasion against harder materials within 24 hours. A linear decrease appears in cell invasion against harder materials after 90 days; softer materials are the opposite. Neurons, astrocytes, and endothelial cells showed stronger invasion and survival in the softer gels [34]. Besides, the viability of different cells depends on the hydrogel rigidity: neurons survived best on hydrogels with

Table 1: Mechanical/rheological properties of the human brain.

	Stiffness	Storage modulus	Loss tangent	Elastic modulus	Viscoelastic shear stiffness
Brain	0.62–2.99 kPa [33]	1.18–2.22 kPa [23]	0.09–0.70 rad [33]	3–10 kPa [23]	2.068 kPa [33]

rigidity less than 1 kPa, while astrocytes survived better on more rigid gels up to 10 kPa [20]. Different conditions require corresponding mechanical properties of the gel to match the brain tissue. However, the mechanical properties of brain tissue vary with age, sex, and disease. As the body ages, for example, brain tissue gradually softens [35]. Additionally, the porosity and pore size of biomaterials have effect on cell migration and control of the diffusion of cell metabolites and media, which are critical factors for cell differentiation and survival. Studies have shown that 90% of the pore and aperture between 10 and 100 μm is the most suitable for the nerve cells (neurons) growth [36, 37].

2.3. Electrical Properties. Biological electrical stimulation is critical to the nervous system signal transduction involved in neurotransmitter-dependent interactions between neurons. The electrical conductivity of the human brain is between 0.63 and 2.43 mS/cm, and the speed of signal transduction is around 7000 m/s [38]. At present, many conductive materials have witnessed application to the regeneration of the CNS after injury. Implantable biomaterials contain a small number of neurons with a long distance between them. Conductive biomaterials can mimic the neurotransmitters produced between healthy neurons, increasing the electrical conductivity of neurons [39]. Besides, the study of the effect of electric charge on the culture and differentiation of nerve cells in carbon nanotubes (CNTs) with semiconductor properties found that the chemical effect of electric charge (such as positive, negative, and neutral charge) on cells growth, proliferation, or differentiation [40]. Studies of hydrogels also found that polypropylene fumarate glycol (P (PF-co-EG) hydrogel combined with positively charged arginine polymer proved that the cells number on the hydrogel increased, which was demonstrated by increasing the glucosin content on the hydrogel, indicating that positively charged hydrogels contribute to cell proliferation [41]. Another set of experiments encapsulated the mouse embryonic stem cells in FN, alginate or alginate–HA. The synaptic types and different neuron subtype markers demonstrated the increased differentiation of neurons in negatively charged alginate or alginate-HA, suggesting the promotion of negatively charged materials on the differentiation of neural stem cells to some extent [42].

2.4. Biodegradability and Biocompatibility. Biodegradable materials are becoming increasingly popular by avoiding secondary surgery damage. The biomaterial degrades gradually in repairing the damage before being replaced by regenerated tissue, providing a long enough time to allow cell penetration and support axial regeneration [43]. Noticeably, the degradation products of biomaterials must be nontoxic [13]. Besides, biomaterials should present long-term biocompatibility with host tissues, and neither the parent material nor any degradation byproducts should generate host immune responses [44]. The biocompatibility directly determines the immune rejection degree in the host after implantation of biomaterial. Lower immune rejection may reduce inflammation and damage to normal host tissues [45]. This is particularly significant when using synthetic biomaterials affected by complex degradation patterns.

3. Injectable Hydrogels in Repairing Brain Damage

Injectable hydrogel polymers widely used in brain injury repair research fall into natural materials and synthetic materials. The most commonly used natural hydrogel materials in tissue engineering are based on the natural components of ECM, such as hyaluronic acid, collagen, alginate, chitosan, cellulose, gelatin, and others [46–49]. Except for higher biocompatibility and degradation rates, they are more readily available and more active in stimulating cell biological function. However, the shortcomings of natural hydrogels are also noteworthy, such as the heterogeneity of materials in different batches, difficulty in precise customization of the material's various properties, and the possibility of carrying natural pathogen of the immune response [50]. Therefore, synthetic polymer hydrogels have received extensive attention. Nowadays, hydrogels of synthetic materials widely used in CNS are usually composed of polymers such as polyethylene glycol (PEG), poly-N (2-hydroxyl) methyl acrylamide (PHEMA), or poly-N-2-hydroxylacrylamide, methyl acrylamide (PHPMA) [51–53]. Compared with natural materials, various critical parameters of synthetic hydrogels are more controllable to better adapt to the intracranial injury environment.

Self-assembled hydrogels are an important type. Unlike the covalent bonding between monomers in traditional hydrogels, the monomer units of self-assembled hydrogels often connect by internal noncovalent forces, thus presenting soft and deformable mechanical properties [54]. The random internal structures enable the formation of self-assembled hydrogels when the environmental pH or temperature changes. Such property allows self-assembled hydrogels to be easily injected into diseased areas and recoagulated into a gel [55]. Most injectable hydrogels are hydrophilic and easily mix with cells. A significant role of injectable hydrogels is to serve as carriers for implanted cells and provide favorable cell growth and differentiation environment. Besides, the use of hydrophobic materials such as PLGA requires different procedures to deliver cells [56].

3.1. Application of Natural Injectable Hydrogels in Brain Damage Repair

3.1.1. Injectable ECM. Injectable hydrogels composed of native ECM have many advantages, such as three-dimensional

structure, low immunogenicity, various biomolecules in the components, and the retention of many cytokines and chemicals that promote cell growth and differentiation [57–59]. The preparation of injectable ECM generally depends on digesting ECM with pepsin and decellularization. The materials used to prepare ECM hydrogels for repairing CNS injuries fall into nerve tissues (pig brain and spinal cord) and nonnerve tissues (pig bladder, human umbilical cord) [60–62]. In a series of studies, Ghuman et al. prepared ECM from pig bladder. Then, the ECM was exposed to 4% ethanol, decellularized in 0.1% acetic acid, and lysed with pepsin to form an injectable fluid at room temperature of 21°C. Different concentrations of ECM hydrogels were injected into the brain of apoplexy rats to estimate the biodegradation rate of the materials, the penetration degree of endogenous cells and nerve cells into the materials, and the degree of tissue modification around the apoplexy cavity. These studies conclusively demonstrated that 4 mg/mL injectable ECM hydrogel could induce maximum brain tissue regeneration. At this concentration, 80% ECM hydrogel degraded at a rate of 6.11 μL/day 14 days after implantation. The infiltration level of macrophages in hydrogel could maintain at $700 \times 800/\mu$L. After 90 days of injection, the density of mature nerve cells continued to increase in the remaining hydrogel [30]. This is a sign of the regeneration and transformation of the tissue structure (Table 2).

3.1.2. Hyaluronic Acid. Hyaluronic acid (HA) is a highly aqueous polylinear polysaccharide consisting of repeated, alternating disaccharide units. This polysaccharide is found in components of the extracellular matrix (ECM) in tissues throughout the body, especially in the brain [74–76]. Currently, HA has been recognized as a cornerstone for the creation of new biological materials, as a carrier for cell transplantation or as a stand-alone biological scaffold because HA is both biocompatible and biodegradable. Moreover, the properties can undergo various modifications [77, 78]. Some studies prepared HA-based hydrogels by Michael addition between acrylate in the main chain of HA and crosslinked peptides of MMPase. Varying the number of different cross-linking agents could achieve mechanical properties similar to the brain [63]. Also, the experiment to inject human pluripotent stem cells (iPS-NPC) into the infarcted cavities of stroke mice filled with or without hydrogel found that hydrogel did promote differentiation of iPS-NPC cells, though the hydrogel did not improve cell survival after one week of stem cell transplantation.

Cook et al. injected the combination of injectable HA hydrogel and brain-derived neurotrophic factor (BDNF) into the cranial cavity of the mouse one week after stroke. Nine weeks after stroke, the number of new neurons was significantly higher in the hydrogel-plus BDNF group than in the control group [64]. In separate work, the researchers successfully developed a novel enzyme-crosslinked injection hydrogel consisting of a combination of hyaluronic acid (HYA), dopamine (DA), and 3- (4-hydroxybenzene) acrylic acid (HPA).

The concentration range of HRP, H2O2, and polymer could control the gelation time of HYA-DA-HPA hydrogel from 3 s to 5 minutes. In some specific cases, the use of HRP and H2O2 as coupling catalysts could achieve 3 s gelation of hydrogels in physiological conditions. HYA is an essential component of the extracellular matrix of the CNS, and DA can restore dopaminergic neurons. Stem cell transplantation by injectable HYA-DA-HPA hydrogel is a potential therapeutic strategy for CNS repair and regeneration [23]. Besides, hyaluronic acid/methylcellulose (HAMC) hydrogel, a physical cross-linking hydrogel based on HA, has seen a broad application in CNS damage. Researchers delivered erythropoietin (EPO) via HAMD hydrogels to the cerebral cortex of mice with stroke. The result found decreased inflammatory response reduced, shrunken stroke lumen, increased number of neurons surrounding the infarction, and increased migratory neuroblasts in the inferior ventricle area [65]. Ho et al. also confirmed the role of HAMC hydrogels in the CNS [66] (Table 2).

3.1.3. Chitosan. Chitosan is a natural polymer composed of D-glucosamine and N- acetyl -D- glucosamine units, incorporating biocompatibility, biodegradability, anti-inflammation, and oxidation resistance [79–82]. However, the poor mechanical properties and low solubility at physiological pH require functionalization for chitosan-based biomaterials. For example, the injection of chitosan hydrogels bound with ferulic acid/succinic into the intracranial cavity of Wistar rats with TBI demonstrated good biocompatibility, suggesting an application potential for CNS injury repair [67]. A study by Tseng et al. in 2015 proposed the first synthesis of self-healing injectable hydrogel based on chitosan with a modulus of 1.5 kPa. This hydrogel exhibited strong injectability and gelatinized slowly at room temperature (>220 s) but rapidly at 37°C (<100 s) [68]. Injecting this self-healing hydrogel resulted in approximately 38% nerve recovery in a zebrafish embryo model of nerve injury. This self-healing hydrogel coating neurosphere-like progenitors could achieve an approximately 81% recovery effect [21]. Based on chitosan, hydroxy cellulose, hyaluronic acid, and β-glycerophosphate, Yao and colleagues developed an injectable composite thermal hydrogel with rapid gelation rate and good biocompatibility at average body temperature. This hydrogel carrying human umbilical cord neural stem cells (hUC-MSC) promoted the survival and proliferation of the endogenous neuron by secreting BDNF and inhibiting apoptosis and facilitated the functional recovery in the rat TBI model [69].

3.1.4. Collagen/Gelatin. Collagen is an extracellular matrix (ECM) protein, the product of further hydrolysis of gelatin [83]. The most common are type IV collagen and type I collagen. With a wide presence in the adult nervous system, type IV collagen is a critical component of the basement membrane and neuromuscular junction of the blood-brain barrier (BBB) [77, 84]. Type I collagen involves axonal growth and neural development, as well as the formation of the dura and pia maters, usually obtained from rat tails or pig and cow skin [34, 85, 86]. Collagen is a good candidate for brain tissue regeneration for its role in the development of the CNS. Guan et al. injected human bone marrow-derived mesenchymal stem cells (hMSCs) collagen hydrogel into the injury site in

Table 2: Natural materials injectable hydrogel applied in brain injury.

Material	Application in brain injury	Characteristics
Injectable ECM [30]	Stroke	Biodegradability and inducing brain tissue regeneration
Hyaluronic acid [23, 63–66]	Stroke, TBI	Biocompatibility, biodegradability, and promotion of ips-NPC differentiation
Chitosan [21, 67–69]	TBI	Biocompatibility, biodegradability, anti-inflammation and antioxidant, and self-healing
Collagen [70–72]	TBI, Parkinson	Reducing the spread of transplanted cells to nonspecific organs and promoting the growth and differentiation of NSC
Fibrin [44, 73]	Alzheimer's disease, TBI	Reducing inflammation and providing a suitable living environment for cells

experimental TBI rats [70]. The results demonstrated a better therapeutic effect of collagen hydrogel combined with HMSCs than HMSCs alone. The placement of collagen hydrogels minimized the proliferation of transplanted cells to nonspecific organs and supported cell growth and differentiation. Finally, the brain metabolism of the experimental rats improved, and the brain function was restored. A study on Parkinson's disease injected the rat NSC suspended in a collagen hydrogel precursor solution into the striatum of healthy rats [71]. The results demonstrated the excellent viability of NSC in collagen hydrogels. The NSC could be reabsorbed after 15 days, suggesting biodegradability. Hovan et al. responded to neurodegenerative diseases by delivering neurotrophic factors (GDNF) to the brain via transgenic bone marine-derived mesenchymal stem cells (MSCs), employing type I collagen hydrogels as transplant vectors. The results found that hydrogel reduced the response of microglial cells to the graft and the recruitment of astrocytes without affecting cell survival and GDNF secretion [72].

Additional studies have employed injectable gelatin-hydroxy propionic acid (GTN-HPA) hydrogels to support endogenous and transplanted neural stem cells (NSC) in brain injury sites. Except for the similar storage modulus to that of the brain, this hydrogel shows good cellular compatibility with NSC, promoting cell adhesion [87]. Another study on gelatin hydrogels synthesized and optimized injectable gelatin hydrogels crosslinked in situ by glucose oxidase (GOX) and horseradish peroxidase (HRP) and investigated the therapeutic effect of the hydrogels on the inclusion of bone mesenchymal stem cells (BMSCs) in TBI rats [88]. The hydrogels can achieve better cytocompatibility and minimize the immune response in vivo by changing the GOX content. Significantly, this hydrogel loaded with BMSC could promote the survival and proliferation of endogenous nerve cells by inhibiting apoptosis and nutrient supply and accelerate the healing process of damaged areas, thus promoting the nerve function recovery in the rat model of TBI. These findings suggest the great potential of this injectable gelatin hydrogel for TBI therapy and other nerve injury regeneration strategies.

3.1.5. Fibrin. Fibrin is a natural enzyme-degrading protein produced by the partial lysis of fibrinogen by thrombin and involved in the coagulation process of blood and lymph. Fibrin obtained from autologous blood is highly biocompatible [89–92]. However, the fibrin or the increase in plasminase activity caused by fibrin can lead to neuroinflammation [93]. Therefore, it should be cautious when using fibrin as a biomaterial for brain injury repair. Fibrin hydrogels have seen broad applications in spinal cord injury repair [94–98], but few in brain damage. Some researchers developed an in-situ silk fibroin hydrogel by inducing silk fibroin solution with ultrasound and made the material more compatible with the brain by controlling the intensity and time of ultrasound [44]. After intracranial injection of silk fibroin hydrogel in mice, the results only detected transient inflammation and cell death in the implanted area and no cognitive or sensory-motor deficits, suggesting the biosafety of silk fibroin hydrogels in the brain. Another study proved that fibrin-based biological scaffolds could provide a suitable living environment for transplanted cells after brain injury and exert an antiapoptotic effect on nerve cells [73].

3.2. Application of Synthetic Injectable Hydrogels in Brain Damage Repair. The synthetic injectable hydrogels primarily are polyacrylamide- (PAM-) based and PEG-based hydrogels. Compared with the natural hydrogel, such hydrogels show worse physical properties seemingly and cause inflammatory reaction more likely after in vivo injection [99, 100] (Table 3). In an in vivo study, Tamariz et al. injected PEG-Si, a thixotropic hydrogel with irradiation silica nanoparticles, into the striatum region of rats while injected sterile saline solution into the other cerebral hemisphere [101]. After 30 days, significant validation and astro colloid reaction appeared in the hemisphere where the polymer hydrogel was injected. However, the situation is not without solutions. In 2008, Bjugstad et al. implanted PEG-based hydrogels into the striatum and frontal cortex of primates [102]. PLA-B-PEG-B-PLA Triblock Polymer performed photo crosslinking by a methacrylate group to form a hydrogel. One hemisphere of the grivet brain was injected with hydrogel, and the contralateral hemisphere was injected with a needle without hydrogel as the sham-implantation group. A third grivet received bilateral injections of PEG-GDNF. All the hydrogels had completely degraded after four months. 13% W/V of PEG hydrogel induced minimal astrocyte and microglial infiltration, which was even similar to that of the sham-implantation group. In comparison, 20% W/V PEG loaded with GDNF only slightly increased the glial response, suggesting that PEG-based hydrogels could still be a promising drug delivery system after modification.

Table 3: Synthetic materials injectable hydrogel applied in brain injury.

Material	Application in brain injury	Characteristics
PEG [101, 102]	Alzheimer's disease	Biocompatibility, biodegradability, reduction of inflammation, induction of brain tissue regeneration
HEMA [103]	TBI	Stimulate neural differentiation
PU [104]	TBI, neurodegenerative diseases	Stimulate neural differentiation

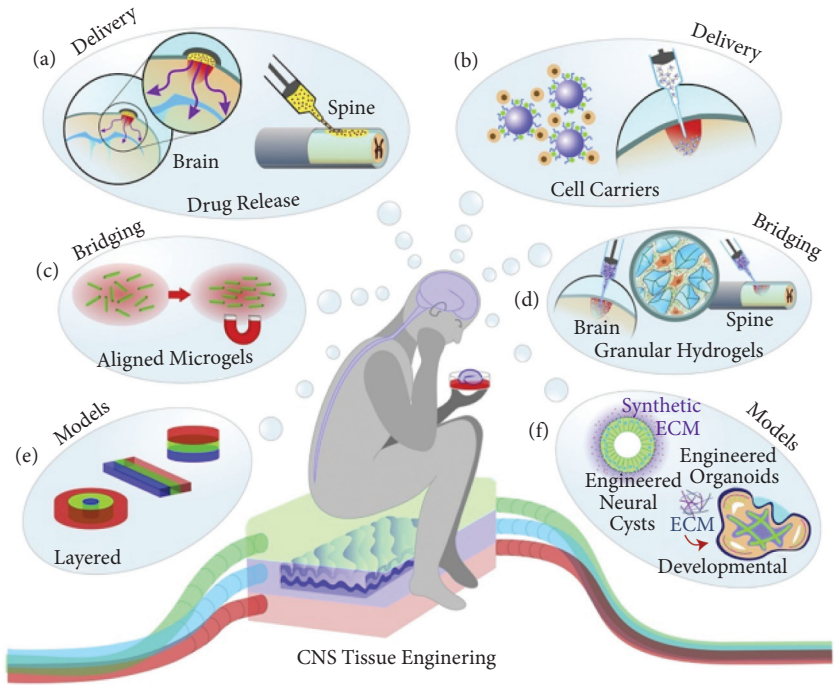

Figure 2: Hydrogels in CNS models and therapy. (a) Hydrogels have been proposed for use in controlled release of soluble factors for drug delivery applications, (b) as carriers that support cell transplantation, (c) as alignment that guides axon growth direction, and (d) as bridge composed of granular gels and microgels. (e) Layered hydrogels have been used to spatially compartmentalize neurons to replicate aspects of in vivo tissue structure. (f) The hydrogel has been used as an in vitro development model [27] (Copyright 2020, with permission from Elsevier).

3.3. Application of Self-Assembled Hydrogels in Brain Damage Repair. In recent years, self-assembled hydrogels have received increasing research interest. Self-assembled hydrogels consist of natural, synthetic, or mixed hydrogels, able to bind to self-assembled proteins [105–107]. Self-assembled peptides (SAP) are the primary type of self-assembled hydrogels. They have short, repeated amino acid units and altered polar and nonpolar residues, which allow them to form a double-β-plate structure when dissolved in water [108]. This structure enables SAP to undergo sol-gel transformation without toxic cross-linking agents and chemical substances, exhibiting natural biocompatibility [109, 110]. The sol-gel transformation of SAP mostly occurs under physiological conditions, such as pH 7.4, temperature 37°C, and others, [55, 111] enabling SAP to be an ideal material for biohydrogels. The different self-assembled structures and gel triggers divide many self-assembled peptide hydrogels into ionic complimentary hydrogels, peptide amphiphile hydrogels, π–π stacking hydrogels, β3-peptide hydrogels, and others [112–115]. Guo et al. implanted an ionic complimentary hydrogel RADA16 into the lesion cavities of surgically induced TBI rats to investigate the potential to reconstruct damaged cortex. RADA16 successfully integrated with host tissue and significantly reduced the size of the lesion cavity after six weeks. Besides, highly pathological glial hyperplasia and reduced inflammatory response were also observed [116]. Also, SAP hydrogel could deliver exogenous stem cells into the brain. Researchers attached IKVAV, a laminin adhesion motif, to RADA16 and encapsulated NSC into RADA16. Then, the combination was transplanted into rats that had suffered damage to the neocortex from a perforated biopsy. After six weeks, the encapsulated NSC proliferated and differentiated into neurons, and the expression of mature neuronal markers, such as β-tubulin and MAP2, increased compared to the formation of cell therapy alone. Synapsin-1 levels, a potential marker of synaptic formation, also increased [55]. Besides, many experiments have also shown that SAP could transport drugs, biological agents, and other therapeutics into the brain damage cavity to improve the treatment efficiency with good biocompatibility [117–119].

3.4. Others. Injectable hydrogel-based devices with tailored properties and integrated functionalities have gradually provided new ideas for many refractory brain injury diseases [120]. These injectable products are not limited to using a specific natural or synthetic material but an interpenetrating polymer network (IPN) composed of various materials to serve as a delivery system for various macromolecule components. The mechanical/rheological and functional features of the polymer network can be adjusted according to the properties of different components. Marta Tunesi et al. proposed a delivery system consisting of a semi-interpenetrating polymer network (semi-IPN) prepared by promoting collagen (COLL) fibrillogenesis in the presence of hyaluronic acid (HA) and loaded with gelatin particles. Researchers loaded the selected COLL-LMW HA composites with Tat-Hsp70 finally conveying neuroprotection in an in vivo model of dopaminergic degeneration [121]. Semi-interpenetrating polymer networks (semi-IPNs) based on collagen and poly(ethylene glycol) (PEG) were also investigated to solve the problem of neurodegenerative disorder [99].

Additionally, the combination of nanomaterials and injectable hydrogels could also be utilized to deliver complex drugs and cells within the brain, which could be very helpful in the treatment of degenerative brain diseases and brain damage. With the help of nanomaterials, intranasal administration can be achieved to enhance the brain's targeting of neuroprotective molecules [122].

4. Conclusions and Prospects

The discussion of the hydrogel as a biological scaffold treating CNS injuries has continued for years. However, the continuous updating of clinical treatment methods for brain injury suggests the minimally invasive treatment with a small window as an increasing trend. The traditional implanted hydrogel can no longer meet the requirements. Injectable hydrogels can realize in vitro sol-in vivo gel. In vitro, accurate injection of hydrogel with the required cells and drugs into the lesion site through a fine needle and in vivo gelation in the lesion cavity at an appropriate speed can minimize lesion cavity, promote nerve tissue regeneration, and reduce inflammation (Figure 2). However, the unstable and inaccurate introduction of hydrogel into the body is risky due to the current high technical requirements for injecting hydrogel into the brain and the lack of reports on the procedure. Also, the discovery of the nerve tissue growth stimulation mechanism is insufficient. Therefore, except for encouraging researchers to continue the study on the structure and properties of hydrogels, more research should focus on the mechanism behind the tissue response, such as the frontal connection mechanism between hydrogels and axons, to better promote the functional recovery after hydrogel implantation. The related research continues and there are hopes to design the most efficient injectable hydrogel for brain damage repair.

Disclosure

Huiyan Sun and Limin Zhang are the co-first authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Huiyan Sun and Limin Zhang have made the same contribution to the article.

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