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HYDROGEL-BASED BIOMATERIALS IN CENTRAL NERVOUS SYSTEM REPAIR: MECHANISMS, CELLULAR INTERACTIONS, AND TRANSLATIONAL CHALLENGES

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Abstract

Injuries of the central nervous system (CNS), such as stroke, traumatic brain injury, and spinal cord injury, are associated with limited intrinsic regenerative capacity and poor functional recovery. Hydrogel-based biomaterials have gained increasing attention as therapeutic platforms capable of addressing the multifactorial pathophysiology of CNS damage. Owing to their high water content, tunable mechanical properties, and extracellular matrix–mimicking characteristics, hydrogels provide structural support while actively modulating cellular behavior and the post-lesional microenvironment. This review examines the fundamental mechanisms underlying hydrogel–cell interactions, including mechanotransduction, biochemical signaling, and immunomodulation, and highlights their role in promoting neural survival, axonal regeneration, and synaptic reorganization. Particular emphasis is placed on injectable and hyaluronic acid–based hydrogels, as well as their application as delivery systems for neural stem cells and bioactive molecules. Finally, key translational challenges, including safety, scalability, and regulatory considerations, are discussed alongside emerging directions such as smart hydrogels and personalized regenerative strategies. Collectively, hydrogel-based biomaterials represent a promising and versatile approach for advancing CNS repair toward clinical implementation.

Keywords: hydrogels, central nervous system repair, neural tissue engineering, biomaterials, neuroregeneration

Pathophysiology of central nervous system injury and rationale for hydrogel-based interventions

Injuries of the central nervous system (CNS), including ischemic stroke, traumatic brain injury (TBI), and spinal cord injury (SCI), are characterized by a complex and highly orchestrated pathophysiological cascade that severely limits spontaneous regeneration and functional recovery. Unlike peripheral nervous tissue, the CNS exhibits a markedly restricted regenerative capacity, largely due to the hostile post-lesional microenvironment, inhibitory extracellular matrix (ECM) remodeling, and sustained neuroinflammation [1]. These factors collectively justify the exploration of advanced biomaterial-based strategies, particularly hydrogel-based systems, aimed at recreating a permissive milieu for neural repair.

The initial mechanical or ischemic insult triggers a primary injury, followed by a secondary phase involving excitotoxicity, oxidative stress, disruption of the blood–brain or

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blood–spinal cord barrier, and infiltration of inflammatory cells [2]. This secondary injury phase is clinically relevant, as it expands tissue damage beyond the original lesion core and contributes significantly to neuronal loss and axonal degeneration. Concurrently, reactive astrocytes, microglia, and infiltrating macrophages orchestrate a chronic inflammatory response that culminates in glial scar formation, a structural and biochemical barrier to axonal regrowth [3].

From a structural perspective, CNS injury is associated with extensive degradation of the native ECM. Components such as hyaluronic acid (HA), proteoglycans, and glycoproteins are either excessively degraded or aberrantly deposited, altering the biomechanical and biochemical cues essential for neural cell survival and migration [4]. The loss of a functional ECM not only deprives neural cells of structural support but also disrupts critical cell–matrix signaling pathways that regulate differentiation and synaptic integration. Consequently, therapeutic strategies that merely target neurons without addressing the surrounding matrix have shown limited efficacy [5].

Hydrogel-based biomaterials have emerged as promising candidates to address these multifactorial challenges. By definition, hydrogels are three-dimensional, water-swollen polymeric networks capable of mimicking key features of native neural ECM, including high water content, viscoelasticity, and diffusivity [6]. Their tunable physicochemical properties allow precise modulation of stiffness, porosity, and degradation kinetics, parameters known to influence neural progenitor cell fate and axonal extension [7]. Importantly, hydrogels can be engineered to match the exceptionally soft mechanical properties of brain and spinal cord tissue, thereby avoiding mechanotransductive signals that would otherwise promote glial activation or inhibit neuronal differentiation [8].

Another major rationale for hydrogel-based interventions lies in their ability to conform to irregular post-injury cavities. Following stroke or traumatic injury, tissue necrosis often results in cystic cavities that lack intrinsic regenerative potential. Injectable hydrogels can be delivered minimally invasively and polymerize in situ, providing immediate structural continuity while minimizing additional tissue damage [9]. This feature is particularly advantageous in CNS applications, where surgical trauma must be strictly limited.

Beyond mechanical support, hydrogels actively modulate the post-lesional microenvironment. Certain formulations exhibit intrinsic anti-inflammatory properties or can attenuate astrocytic reactivity, thereby reducing glial scar density and permissiveness to axonal growth [10]. Moreover, hydrogels can serve as reservoirs for bioactive molecules, enabling sustained and localized delivery of growth factors that counteract inhibitory signals present in the injured CNS [11]. This capacity is critical given the short half-life and systemic side effects associated with conventional growth factor administration.

The rationale for hydrogel use is further reinforced by its compatibility with cell-based therapies. Transplanted neural stem or progenitor cells often exhibit poor survival when injected alone, due to anoikis, inflammatory stress, and lack of matrix anchorage. Encapsulation within hydrogels improves cell viability, promotes controlled differentiation, and enhances integration with host tissue [12]. This synergistic interaction between biomaterial scaffolds and cellular therapies aligns with contemporary tissue engineering paradigms that emphasize the reconstruction of functional neurovascular niches rather than isolated neuronal replacement [13].

Despite encouraging preclinical evidence, the translation of hydrogel-based therapies to clinical practice remains challenging. Variability in injury models, species-specific responses, and difficulties in standardizing biomaterial properties complicate comparative analysis and regulatory approval [14]. Nonetheless, the convergence of advances in polymer chemistry, neurobiology, and regenerative medicine continues to strengthen the scientific rationale for hydrogels as central components of next-generation CNS repair strategies [15].

Design and physicochemical properties of hydrogels for CNS repair

The successful application of hydrogel-based biomaterials in central nervous system (CNS) repair critically depends on rational design principles that integrate physicochemical properties with the unique biological and mechanical requirements of neural tissue. Injectable hydrogels have gained particular relevance due to their minimally invasive delivery and capacity to form three-dimensional matrices in situ, features that are essential for treating delicate and structurally complex CNS lesions [15].

From a compositional standpoint, hydrogels used in neural tissue engineering may be broadly classified into natural, synthetic, or hybrid systems. Natural polymers such as hyaluronic acid (HA), collagen, and gelatin are favored for their intrinsic biocompatibility and biochemical similarity to native extracellular matrix (ECM) components [16]. Among these, HA occupies a central role in CNS applications, as it is abundantly present in the developing and adult brain, where it regulates cell migration, proliferation, and synaptic plasticity. HA-based hydrogels can be chemically modified to introduce cell-adhesive motifs or degradable crosslinks, allowing precise control over cell–matrix interactions without compromising biological relevance [17].

Table 1. Design parameters and physicochemical properties of hydrogels for CNS repair

Design parameter	**Characteristics**	**Relevance for CNS repair**
Polymer composition	Natural (hyaluronic acid, collagen), synthetic, hybrid	Mimics native ECM, enhances biocompatibility and neural cell interaction
Mechanical stiffness	Low elastic modulus (≈100–1000 Pa)	Matches brain and spinal cord mechanics, promotes neuronal differentiation
Porosity and diffusivity	Interconnected porous networks	Facilitates nutrient, oxygen, and signaling molecule transport
Degradability	Enzymatic or hydrolytic, tunable kinetics	Allows gradual tissue remodeling and scaffold replacement
Injectability	In situ gelation (chemical or thermal)	Enables minimally invasive delivery and cavity conformation
Biofunctionalization	Adhesive peptides, degradable crosslinks	Enhances cell adhesion, migration, and matrix remodeling

Table 1 summarizes the key design and physicochemical parameters of hydrogels used for central nervous system repair. Optimization of composition, mechanical properties, porosity, and degradation kinetics is essential for recreating a permissive neural microenvironment.

Physicochemical properties, particularly mechanical stiffness, represent a key determinant of hydrogel performance in CNS repair. Neural tissues are characterized by exceptionally low elastic moduli, typically in the range of hundreds of pascals. Hydrogels with stiffness values exceeding this range may inadvertently promote astrocytic differentiation or glial activation, thereby counteracting regenerative efforts [18]. Consequently, the ability to fine-tune hydrogel viscoelasticity to match native CNS tissue is considered a prerequisite for functional integration. HA-based systems are particularly advantageous in this regard, as their mechanical properties can be modulated through polymer concentration, molecular weight, and crosslinking density.

Porosity and diffusivity constitute additional design parameters of major relevance. An optimal hydrogel scaffold must permit efficient diffusion of oxygen, nutrients, and signaling molecules while simultaneously supporting cellular infiltration and axonal extension. Excessively dense networks may restrict molecular transport, whereas overly porous matrices may lack structural integrity and degrade prematurely [19]. Balancing these opposing

requirements remains a central challenge in hydrogel engineering, especially in the context of long-term CNS repair.

Degradability is another critical feature influencing hydrogel performance and biocompatibility. Ideally, degradation kinetics should be synchronized with tissue remodeling, allowing gradual replacement of the scaffold by newly formed neural and glial elements. In HA-based hydrogels, degradation can be mediated enzymatically by hyaluronidases or controlled through hydrolytically labile crosslinks, enabling predictable and tunable resorption profiles [20]. Importantly, degradation byproducts must be non-toxic and should not elicit secondary inflammatory responses, a consideration of particular importance in the immunologically sensitive CNS environment.

Injectability and in situ gelation further distinguish hydrogels from preformed solid scaffolds. Thermoresponsive or chemically crosslinkable hydrogels can be delivered as liquids and subsequently solidify within the lesion cavity, ensuring intimate contact with host tissue and minimizing dead space formation. This property is especially valuable in irregular post-stroke or post-traumatic cavities, where precise geometric matching is otherwise difficult to achieve [15].

In conclusion, the design of hydrogels for CNS repair requires a delicate balance between biological mimicry and engineering control. By tailoring composition, mechanical behavior, porosity, and degradation kinetics, hydrogel-based biomaterials can be optimized to recreate key aspects of the native neural microenvironment. Such rationally designed systems provide a robust platform for subsequent cellular and molecular therapies, reinforcing their central role in contemporary strategies for CNS regeneration.

Cell–hydrogel interactions and mechanisms of neural regeneration

The regenerative potential of hydrogel-based biomaterials in central nervous system (CNS) repair is primarily dictated by their capacity to establish dynamic and biologically relevant interactions with neural cells. Rather than acting as inert fillers, hydrogels function as artificial extracellular matrices (ECM) that provide mechanical support, biochemical signaling, and spatial guidance essential for neural repair processes [3,14].

Neural stem cells (NSCs) and neural progenitor cells (NPCs) are highly sensitive to the physicochemical properties of their surrounding matrix. Substrate stiffness, in particular, exerts a decisive influence on cell fate determination. Hydrogels with elastic moduli closely matching native brain tissue promote neuronal differentiation and neurite extension, whereas increased stiffness biases differentiation toward astrocytic phenotypes, contributing to glial scar formation [8,18]. This mechanosensitive behavior is mediated through cytoskeletal tension and integrin-dependent signaling pathways that translate mechanical cues into transcriptional responses.

Biochemical interactions further refine cell–hydrogel crosstalk. Functionalization of hydrogels with adhesive peptide motifs, such as arginine–glycine–aspartic acid (RGD), enhances cell attachment, migration, and survival by activating focal adhesion complexes [17]. In hyaluronic acid (HA)-based hydrogels, receptor-mediated interactions with CD44 and RHAMM are of particular relevance, as these pathways regulate neural cell motility, proliferation, and lineage commitment during both development and regeneration [19]. Such biomimetic signaling recapitulates key aspects of the native neural ECM and supports endogenous repair mechanisms.

Hydrogels also influence the inflammatory and glial responses that critically shape the post-lesional microenvironment. Reactive astrocytes and activated microglia are major contributors to secondary injury, releasing pro-inflammatory cytokines and depositing inhibitory chondroitin sulfate proteoglycans that impede axonal growth. Experimental evidence indicates that appropriately designed hydrogel matrices can attenuate astrocytic hypertrophy

and modulate microglial activation, thereby reducing glial scar density and creating a more permissive environment for axonal regeneration [4,10].

Axonal guidance and reconnection represent central challenges in CNS repair. Hydrogels can be engineered to provide aligned microstructures or permissive gradients that direct axonal extension across lesion sites. Such structural cues, combined with supportive biochemical signaling, facilitate axon bridging and synaptic reorganization, processes that are otherwise severely limited in the injured CNS [6,20]. These effects are particularly evident in models of spinal cord injury, where hydrogel scaffolds have been shown to support long-distance axonal growth.

The interaction between hydrogels and transplanted cells further amplifies regenerative outcomes. Encapsulation of NSCs or NPCs within hydrogels improves cell retention at the injury site, enhances survival, and promotes controlled differentiation compared to direct cell injection [1,12]. This synergistic relationship underscores the importance of integrating material design with cellular therapy strategies to achieve meaningful functional recovery.

Hydrogels as delivery platforms for cells and bioactive molecules

A defining advantage of hydrogel-based biomaterials in central nervous system (CNS) repair lies in their capacity to function as integrated delivery platforms for both therapeutic cells and bioactive molecules. This dual role directly addresses key limitations of conventional regenerative approaches, namely poor localization, rapid degradation of soluble factors, and low survival of transplanted cells within the hostile post-injury microenvironment [15,16].

Cell-based therapies using neural stem cells (NSCs) or neural progenitor cells (NPCs) have demonstrated significant regenerative potential; however, their clinical translation has been hindered by extensive cell loss following transplantation. Mechanical shear stress during injection, inflammatory mediators, and the absence of extracellular matrix (ECM) support contribute to apoptosis and limited engraftment [1,12]. Hydrogel encapsulation provides a protective three-dimensional niche that buffers transplanted cells from acute stressors, enhances cell retention within lesion cavities, and promotes gradual integration with host tissue [2,14]. In particular, injectable hydrogels enable minimally invasive delivery while ensuring spatial confinement of cells at the target site.

The properties of the hydrogel matrix critically regulate the behavior of encapsulated cells. Parameters such as stiffness, degradation rate, and biochemical functionalization influence cell survival, proliferation, and lineage specification. Hyaluronic acid (HA)-based hydrogels are especially well suited for this purpose, as HA is a native component of the CNS ECM and supports neural cell migration and differentiation through receptor-mediated signaling [17–19]. By modulating crosslink density and molecular weight, HA hydrogels can be tailored to synchronize scaffold degradation with tissue remodeling, thereby facilitating progressive host–graft integration.

In addition to cellular delivery, hydrogels serve as efficient reservoirs for bioactive molecules, including neurotrophic factors, cytokines, and angiogenic mediators. Direct administration of these agents is limited by short half-life, poor tissue penetration, and systemic side effects. Incorporation into hydrogel matrices enables localized and sustained release, maintaining therapeutic concentrations within the lesion site over prolonged periods [11,15]. This controlled delivery is particularly relevant in the CNS, where the blood–brain barrier restricts access of systemically administered molecules.

Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) have been successfully integrated into hydrogels to enhance neuronal survival and axonal outgrowth, while vascular endothelial growth factor (VEGF) supports angiogenesis and metabolic recovery in injured tissue [10,20]. When combined with cell-laden

hydrogels, these molecules exert synergistic effects, simultaneously supporting graft viability and stimulating endogenous repair mechanisms [4].

Emerging strategies further expand the delivery capabilities of hydrogels by incorporating extracellular vesicles, exosomes, or multi-factor release systems that better replicate the complex signaling environment of neural regeneration [5]. Such combinatorial approaches reflect a paradigm shift toward multifunctional biomaterial platforms capable of addressing multiple pathological processes simultaneously.

Table 2. Hydrogel-based delivery strategies for cells and bioactive molecules in CNS repair

Delivery component	**Hydrogel-based strategy**	**Therapeutic effect**
Neural stem/progenitor cells	Cell encapsulation within injectable hydrogels	Improved cell survival, retention, and controlled differentiation
Growth factors (BDNF, NGF)	Sustained release from hydrogel matrix	Enhanced neuronal survival and axonal outgrowth
Angiogenic factors (VEGF)	Localized controlled delivery	Promotion of vascularization and metabolic support
Anti-inflammatory agents	Hydrogel-mediated local modulation	Reduction of glial activation and secondary injury
Extracellular vesicles/exosomes	Encapsulation or adsorption	Paracrine signaling and immunomodulation
Combined cell–factor systems	Multifunctional hydrogels	Synergistic enhancement of neuroregeneration

Table 2 illustrates the multifunctional role of hydrogels as delivery platforms for cells and bioactive molecules in CNS repair, highlighting their ability to provide localized, sustained, and combinatorial therapeutic effects.

Translational challenges and future directions in hydrogel-based cns therapies

Despite substantial progress in the development of hydrogel-based biomaterials for central nervous system (CNS) repair, their translation from experimental models to clinical application remains limited. This gap reflects a combination of biological complexity, technical constraints, and regulatory challenges that must be addressed to fully realize the therapeutic potential of these systems [9,13].

One of the principal translational barriers arises from the heterogeneity of CNS injuries and the variability of preclinical models. Experimental studies often rely on controlled and homogeneous injury paradigms in young, healthy animals, which poorly reflect the clinical reality of human patients presenting with diverse lesion sizes, chronic comorbidities, and delayed intervention timelines [2,10]. Consequently, therapeutic outcomes observed in preclinical settings may not reliably predict clinical efficacy. Standardization of injury models and outcome measures is therefore essential to enable meaningful comparison across studies and to support regulatory evaluation [16].

Safety and biocompatibility represent additional critical concerns. Although many hydrogel formulations demonstrate excellent short-term compatibility, long-term interactions with neural tissue remain incompletely understood. Unpredictable degradation kinetics, accumulation of byproducts, or delayed immune responses may compromise tissue integrity and functional recovery [11,15]. In the CNS, even subtle inflammatory or fibrotic reactions can have profound neurological consequences, underscoring the need for rigorous long-term safety assessments.

Manufacturing and scalability also pose significant obstacles to clinical translation. Hydrogels intended for CNS applications must exhibit highly reproducible physicochemical properties, including stiffness, gelation time, and degradation profiles. Achieving such

consistency at clinical scale is challenging, particularly for complex or biologically derived polymers [6,14]. Furthermore, sterilization procedures may alter hydrogel structure or bioactivity, complicating regulatory approval and commercial deployment.

From a regulatory perspective, hydrogel-based therapies often fall into the category of combination products, integrating biomaterials with cells or bioactive molecules. This classification entails complex approval pathways, as both device- and drug-related standards must be satisfied [1,12]. Clear regulatory frameworks tailored to regenerative biomaterials are still evolving, contributing to prolonged development timelines and increased costs.

Looking forward, future directions in hydrogel-based CNS therapies emphasize the integration of advanced material design with personalized and adaptive treatment strategies. “Smart” hydrogels capable of responding to environmental cues such as pH, enzymatic activity, or inflammatory mediators offer the possibility of dynamic and temporally controlled therapeutic delivery [5,20]. Additionally, advances in 3D bioprinting and microfabrication enable the creation of spatially organized scaffolds that more accurately recapitulate neural architecture and connectivity [7].

Another promising avenue involves patient-specific approaches that account for lesion characteristics and biological variability. Customizable hydrogel formulations, potentially combined with autologous cells or precision delivery of bioactive agents, may enhance therapeutic efficacy while minimizing adverse effects [3,8].

Conclusions

Hydrogel-based biomaterials have emerged as a cornerstone of contemporary strategies for central nervous system repair, offering a unique capacity to simultaneously address the structural, biochemical, and cellular deficits characteristic of CNS injury. By mimicking key properties of the native extracellular matrix, modulating inflammatory and glial responses, and supporting neural cell survival, differentiation, and axonal regeneration, hydrogels function as active regulators of tissue repair rather than passive scaffolds, thereby redefining the paradigm of neuroregenerative interventions.

Despite compelling preclinical evidence, the translation of hydrogel-based CNS therapies into routine clinical practice remains constrained by biological heterogeneity, long-term safety considerations, manufacturing reproducibility, and complex regulatory pathways. Future progress will depend on the rational integration of advanced material design, cell-based and molecular therapies, and clinically relevant models, with increasing emphasis on smart, injectable, and patient-specific hydrogel systems capable of dynamically interacting with the injured neural microenvironment to achieve durable functional recovery.

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