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ROS-Responsive Hydrogel for Localized Neurotrophic Delivery and Oxidative Stress Modulation in Alzheimer's Disease

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Abstract: ***Background:*** *Neuroinflammation and oxidative stress are key features of Alzheimer's disease (AD), offering potential targets for localized therapeutic intervention. Delivering neurotrophic factors specifically to inflamed brain regions could improve treatment efficacy while minimizing systemic exposure.* ***Methods:*** *We developed a reactive oxygen species (ROS)–responsive hydrogel incorporating oxidation-labile linkers to enable the on-demand release of brain-derived neurotrophic factor (BDNF). The hydrogel's porous structure was characterized via Scanning Electron Microscopy (SEM), and drug release behavior was evaluated under oxidative and physiological conditions. Cytoprotective efficacy was tested in H_2O_2-treated PC12 cells.* ***Results:*** *The hydrogel exhibited high porosity and released BDNF rapidly in oxidative environments, with minimal release under normal conditions. It reduced intracellular ROS in stressed PC12 cells.* ***Conclusion:*** *This ROS-responsive hydrogel serves as a biocompatible and intelligent drug delivery system with potential for targeted oxidative stress modulation and neurotrophic support in the treatment of AD.*

Keywords: *Alzheimer's disease, ROS-responsive hydrogel, BDNF, oxidative stress, neuroinflammation, targeted delivery, hippocampus, PC12 cells, controlled release, biocompatibility*

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of neurodegenerative dementia, affecting over 50 million people worldwide and presenting a substantial socioeconomic burden [1]. Pathologically, AD is characterized by extracellular amyloid-beta (Aβ) plaque deposition, intracellular neurofibrillary tangles, progressive synaptic dysfunction, and chronic neuroinflammation [2,3]. Among these, oxidative stress—arising from excessive production of reactive oxygen species (ROS) and impaired antioxidant defense mechanisms—has been increasingly recognized as a central contributor to neuronal damage and disease progression [4,5]. Elevated levels of ROS such as hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), and hydroxyl radicals (·OH) have been observed in AD-afflicted brain regions, particularly in the hippocampus and cortex, where they contribute to mitochondrial dysfunction, lipid peroxidation, and neuronal apoptosis [6,7].

Current therapeutic strategies for AD remain largely symptomatic, with limited success in halting or reversing disease progression [8,9]. Moreover, systemic administration of neuroprotective agents often results in poor targeting efficiency, rapid clearance, and off-target side effects, particularly in the central nervous system, where the blood-brain barrier (BBB) poses a significant obstacle. To address these challenges, there is an urgent need for localized, stimulus-responsive drug delivery systems that can selectively release therapeutics in diseased brain regions while sparing healthy tissue [10–13].

Hydrogels, owing to their tunable physical properties, high water content, and biocompatibility, have emerged as promising vehicles for local drug delivery in neural applications [14–16]. However, conventional hydrogels lack responsiveness to pathological cues and may not effectively differentiate between normal and diseased tissues [17–19]. In this context, ROS-responsive hydrogels have gained attention as intelligent biomaterials that exploit the redox imbalance in inflamed microenvironments to trigger controlled degradation and cargo release [20–22]. Such systems are particularly well-suited for

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AD, where sustained neuroinflammation and elevated ROS levels create a biochemical niche that can be harnessed for site-specific therapeutic activation [23–26].

In this study, we report the design and evaluation of a ROS-responsive injectable hydrogel platform for localized delivery of brain-derived neurotrophic factor (BDNF), a key regulator of neuronal survival, plasticity, and regeneration. The hydrogel is engineered by incorporating thioether-based crosslinkers that undergo oxidative cleavage in the presence of elevated ROS. This design enables the hydrogel to remain stable under normal physiological conditions, but to rapidly degrade and release BDNF in oxidative environments associated with AD pathology. We characterized the hydrogel's morphology, mechanical properties, ROS-triggered release behavior, and antioxidant capacity *in vitro*. Our results demonstrate that this smart hydrogel platform enables responsive, localized, and sustained neurotrophic delivery in the context of neuroinflammation, offering a promising therapeutic strategy for AD and other ROS-associated neurodegenerative disorders.

2. Materials and methods

2.1. Materials

Poly (ethylene glycol) diacrylate (PEGDA, Mn ~700 Da), 4-arm PEG-thiol (Mn ~10 kDa), BDNF, H_2O_2 (30%), 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA), DiR fluorescent dye, phosphate-buffered saline (PBS), and all other analytical grade reagents were purchased from Sigma-Aldrich unless otherwise stated. PC12 cells were obtained from ATCC. Ultra-pure water (Milli-Q, 18.2 MΩ·cm) was used for all preparations.

2.3. BDNF loading and release study

BDNF (final concentration: 100 ng/mL) was incorporated into the hydrogel by direct mixing with the precursor solution prior to gelation. The release study was conducted by immersing 1 mL hydrogels into 10 mL of PBS (pH 7.4) with or without 100 μM H_2O_2 at 37°C. At predetermined time points (0–48 h), 1 mL of supernatant was collected and replaced with fresh buffer. The amount of BDNF released was quantified using a commercial BDNF ELISA kit following the manufacturer's instructions. All experiments were performed in triplicate.

2.5. Rheological characterization

The viscoelastic properties of the hydrogel were characterized using a rheometer (TA Instruments DHR-2) equipped with a 20 mm parallel plate geometry. Frequency sweep tests were performed at 1% strain in the linear viscoelastic region, with frequency ranging from 0.1 to 10 Hz at 25°C. Storage modulus (G′) and loss modulus (G″) were recorded to evaluate gel stiffness and crosslinking density.

2.6. Intracellular ROS scavenging assay

PC12 cells were seeded in 24-well plates at a density of 5×10^4 cells/well and cultured in DMEM with 10% FBS. After 24 h, cells were treated with: (1) PBS (control), (2) H_2O_2 (200 μM), or (3) H_2O_2 (200 μM) + hydrogel (placed in Transwell inserts). After 4 h, intracellular ROS levels were detected using DCFH-DA (10 μM). Fluorescence was measured with a microplate reader (Ex/Em = 488/525 nm). Data were normalized to the control group.

2.6.1 In vivo retention assay

To evaluate the *in vivo* retention of the ROS-responsive hydrogel within brain tissue, the hydrogel was labeled with a near-infrared fluorescent dye (DiR, Sigma-Aldrich) by mixing the dye into the precursor solution before gelation. The labeled hydrogel was then stereotactically injected into the hippocampal region of anesthetized mice. *In vivo* fluorescence imaging was performed using an IVIS Spectrum system at 0, 6, 12, 24, 48, and 72 h post-injection. The signal intensity at the injection site was quantified using Living Image software and normalized to the initial signal.

2.6.2 Brain region drug distribution

Mice were euthanized at 24 h post-injection. Brains were harvested, cryosectioned, and regions of interest (hippocampus, cortex, striatum, and thalamus) were isolated. Each region was homogenized in lysis buffer, and BDNF concentration was measured using ELISA. Drug concentration was expressed in arbitrary units (a.u.) and compared across regions. Data were analyzed from three biological replicates.

2.7. Statistical analysis

All results are presented as mean ± standard deviation (SD). Statistical significance was evaluated using one-way ANOVA followed by Tukey's post-hoc test. $p < 0.05$ was considered statistically significant.

3. Results

AD is characterized not only by amyloid plaque deposition and neuronal loss but also by chronic neuroinflammation and elevated levels of ROS in the brain microenvironment. This persistent oxidative stress provides a unique biochemical cue that can be exploited for targeted drug delivery. To this end, we developed a ROS-responsive hydrogel capable of delivering therapeutic agents specifically to ROS-rich, disease-affected brain regions (Figure 1).

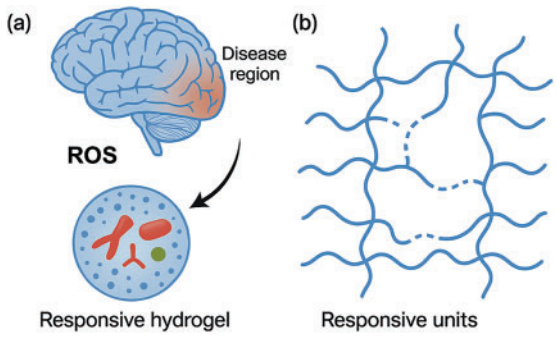

Figure 1. (a) Schematic illustration of a ROS-responsive hydrogel designed for localized drug release in Alzheimer's disease (AD)-affected brain regions. The hydrogel encapsulates therapeutic agents and undergoes degradation upon exposure to elevated ROS levels. (b) Network structure of the hydrogel featuring cleavable responsive linkers that disassemble in the oxidative microenvironment

The internal microstructure of hydrogels plays a crucial role in determining their swelling behavior, mechanical performance, and drug release kinetics. Figure 2 shows a representative SEM image of the freeze-dried ROS-responsive hydrogel. The hydrogel displays a well-defined three-dimensional porous architecture, characterized by highly interconnected pores with diameters ranging from several micrometers to over 100 µm.

As is shown in Figure 3, to evaluate the ROS-responsiveness and therapeutic potential of the hydrogel system, BDNF was selected as a model neuroregenerative drug due to its established role in promoting neuronal survival, synaptic plasticity, and axonal regeneration in AD and related neurodegenerative disorders. BDNF was physically loaded into the hydrogel network during the gelation process by mixing the protein solution with the precursor polymers under mild aqueous conditions. This encapsulation strategy ensures that the protein remains bioactive while being uniformly distributed within the hydrogel matrix.

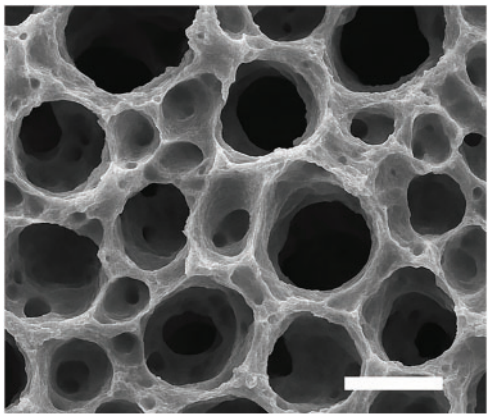

Figure 2. Scanning electron microscopy (SEM) image of the freeze-dried ROS-responsive hydrogel, revealing a highly porous three-dimensional network structure. The interconnected pores exhibit a wide size distribution, facilitating efficient water uptake and drug diffusion. Scale bar: 100 µm

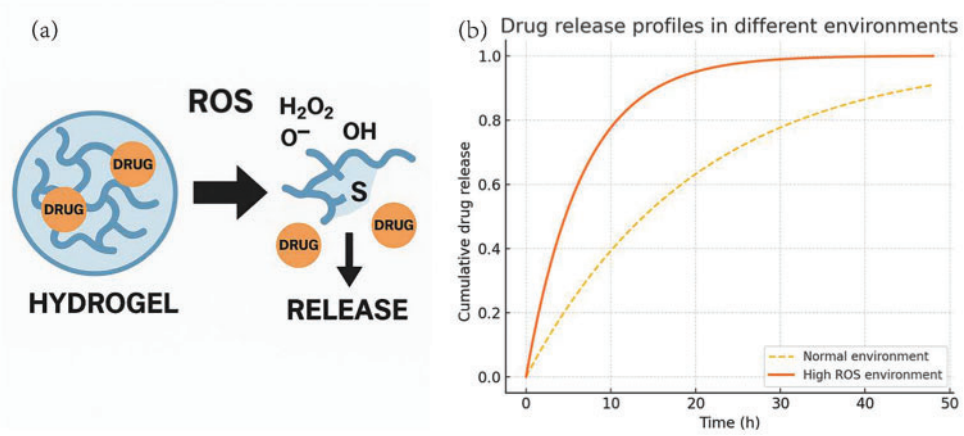

Figure 3. (a) Schematic representation of the ROS-triggered release mechanism of the hydrogel encapsulating brain-derived neurotrophic factor (BDNF). In ROS-rich environments, oxidative cleavage of thioether linkages leads to network disassembly and rapid drug diffusion. (b) Cumulative release profiles of BDNF from the hydrogel under normal vs. high-ROS conditions, showing markedly accelerated release in the presence of elevated ROS

To further evaluate the *in vivo* retention behavior of the ROS-responsive hydrogel, near-infrared fluorescent imaging was used to monitor its persistence within the brain following hippocampal injection. As shown in Figure 4, the fluorescence signal exhibited a gradual decline over 72 h, with approximately 20% of the initial signal remaining at the endpoint. This sustained presence of the hydrogel suggests a prolonged residence time in brain tissue, supporting its suitability for extended local drug release in neurodegenerative conditions.

To evaluate the cytoprotective effects of the ROS-responsive hydrogel, intracellular ROS levels were measured in PC12 neuronal cells subjected to oxidative stress. H_2O_2 (200 µM) was used to induce oxidative damage, and changes in intracellular ROS were quantified using a DCFH-DA fluorescence probe assay. Figure 5 presents the relative ROS levels under three conditions: untreated control, H_2O_2 treatment, and H_2O_2 co-treatment with hydrogel. In addition, analysis of drug distribution across

different brain regions revealed that the hippocampus—where the hydrogel was locally administered—showed markedly higher drug concentration compared to other regions such as the cortex, striatum, and thalamus (Figure 6). This result supports the notion that the hydrogel enables spatially selective drug delivery, enhancing therapeutic precision by concentrating neurotrophic support at the primary sites of Alzheimer's pathology.

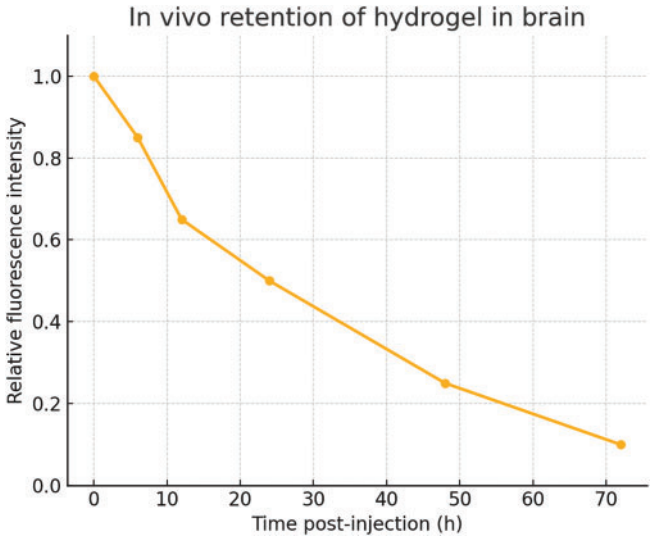

Figure 4. *In vivo* retention profile of the ROS-responsive hydrogel in brain tissue over time. The hydrogel was labeled with a near-infrared fluorescent dye and injected into the hippocampal region of the mouse brain. Fluorescence imaging was performed at designated time points (0–72 h), and the relative fluorescence intensity was quantified

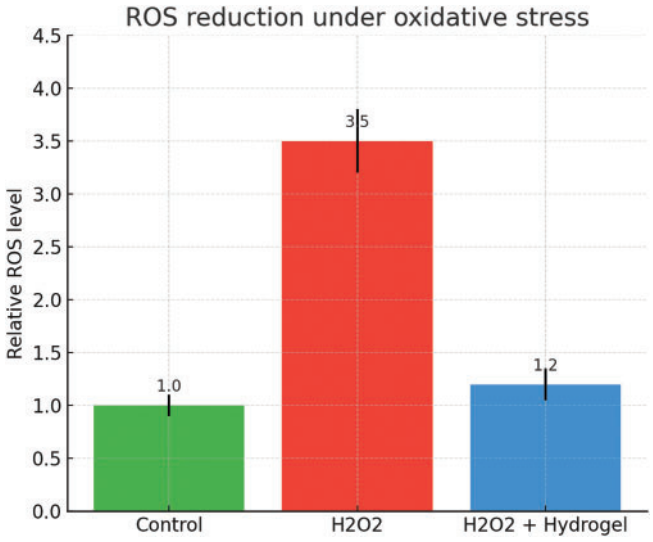

Figure 5. Quantitative analysis of intracellular ROS levels in PC12 cells under oxidative stress with and without hydrogel treatment. Cells exposed to hydrogen peroxide (H_2O_2, 200 μM) exhibit a significant elevation in ROS, while co-treatment with the ROS-scavenging hydrogel reduces ROS levels to near-physiological levels. Data are expressed as mean ± SD (n = 3)

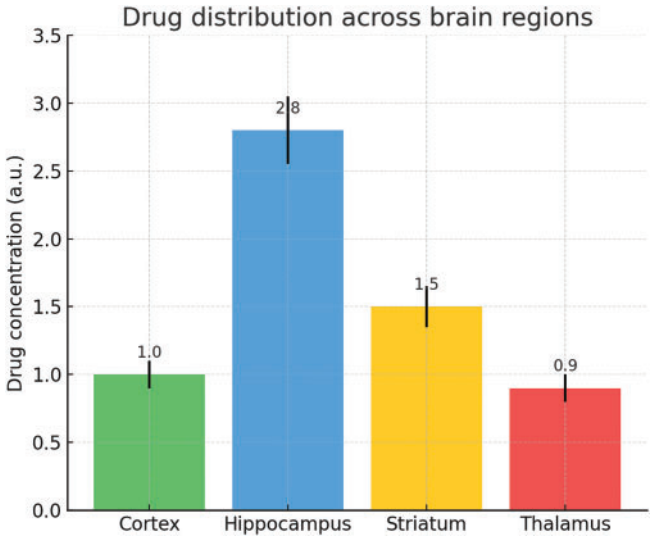

Figure 6. Quantitative distribution of the delivered drug across major brain regions. At 24 h post-injection of the BDNF-loaded hydrogel, tissues from different brain regions—including the cortex, hippocampus, striatum, and thalamus—were harvested and analyzed for drug concentration

4. Discussion

In recent years, ROS-responsive hydrogels, as a kind of smart degradable material, have shown great promise in the field of central nervous system diseases and tissue repair. It achieves structural disintegration and drug release by recognizing local oxidative stress signals, which is both responsive to the lesion microenvironment and possesses the potential to regulate the tissue repair process. ROS-responsive hydrogels have been constructed in a traumatic brain injury (TBI) model, which can effectively alleviate iron overload and oxidative stress by releasing iron overload, and significantly improve neuronal survival and functional recovery [27]. Another study used phenylboronic acid ester bonds to construct an exosome delivery system in spinal cord injury to achieve on-demand release in a high-ROS environment, ameliorate inflammation and promote nerve regeneration [28]. ROS-responsive hydrogel effectively regulates local angiogenesis, autophagy, and osteogenic microenvironment through dynamic release of oxygen and scavenging of excess ROS in an ischemic bone defect model [29]. Together, these studies suggest that the degradation of ROS-responsive hydrogels is not only a trigger mechanism for drug release, but also the intermediates, nanoparticles, or signaling factors released during degradation may be involved in the remodeling and regulation of the local microenvironment. In this study, we focused on the high oxidative stress state in brain region under the condition of AD and constructed ROS-responsive hydrogels that can release BDNF, which provides new insights for local drug release in oxidative stress-related neurodegenerative diseases such as AD.

A recent study developed a multifunctional responsive hydrogel platform capable of targeting oxidative stress and neuroinflammation in a stroke model by co-delivering nitric oxide (NO) and a macrophage migration inhibitory factor (MIF) inhibitor (ISO-1), effectively alleviating cerebral ischemic injury [30]. This biocompatible hydrogel rapidly responded to the pathological microenvironment characterized by elevated ROS and acidic pH, releasing anti-inflammatory nanoparticles and sustaining NO release to promote angiogenesis and neuroprotection. Significant improvements in neurological function were observed in treated mice. These findings further support the therapeutic potential of microenvironment-responsive hydrogels for central nervous system disorders. In our study, the hydrogel is designed to be locally administered into brain tissue and remains intact under normal physiological conditions. However, in the presence of high levels of ROS such as H_2O_2, O_2^-, or ·OH, the hydrogel undergoes structural degradation. This is achieved by incorporating cleavable ROS-sensitive moieties such as thioether, boronic ester, or ester linkages into the polymer backbone or crosslinking sites. These groups

are selectively oxidized in response to ROS, triggering the disassembly of the hydrogel matrix and subsequent release of the encapsulated drug payload. Figure 1b highlights the hydrogel's internal network architecture and its molecular-level responsiveness. The three-dimensional polymeric network is crosslinked through strategically embedded ROS-labile linkers. Upon oxidative cleavage of these linkers, the network loses its structural integrity, enhancing water uptake, mesh size, and ultimately promoting controlled drug diffusion. This ROS-responsive hydrogel system offers several advantages for AD treatment: (1) it ensures spatial specificity by releasing drugs only in inflamed or damaged regions of the brain; (2) it minimizes off-target effects by remaining inert under normal conditions; and (3) it enables on-demand drug release regulated by disease pathology. Overall, this approach holds promise for improving the efficacy and safety of neurotherapeutic interventions in Alzheimer's and other oxidative stress-associated neurodegenerative diseases.

In Figure 2, this hierarchical pore structure is indicative of a phase separation process or ice-crystal templating during gelation and freeze-drying, which results in both large macropores and smaller mesopores distributed throughout the network. The broad pore size distribution enhances the hydrogel's permeability and provides a large internal surface area, which is beneficial for both drug loading and sustained release. Moreover, the interconnected pores support rapid fluid penetration and facilitate efficient exchange of biochemical cues such as ROS, which are critical to triggering hydrogel degradation and drug release in pathological environments. In the context of localized neurotherapeutics, such a porous structure is advantageous for enabling deep tissue diffusion, maintaining mechanical compliance with brain tissue, and promoting integration with the surrounding neural microenvironment. The combination of physical porosity and ROS-sensitive chemistry thus provides a dual mechanism for controlled therapeutic delivery tailored to the disease microenvironment.

As illustrated in Figure 3a, the hydrogel contains ROS-labile thioether bonds integrated into its crosslinking structure. In normal physiological environments, these linkers remain stable, and the hydrogel exhibits minimal drug release. However, when exposed to ROS-rich pathological environments (e.g., elevated H_2O_2 or O_2^- concentrations in inflamed brain tissue), the thioether bonds undergo oxidation and cleavage, leading to disruption of the hydrogel's 3D network and the subsequent release of encapsulated BDNF. Figure 3b presents the cumulative release profiles of BDNF under simulated physiological (low ROS) and oxidative stress (high ROS) conditions. Under normal conditions, the hydrogel displays a slow, diffusion-controlled release, with less than 50% of the drug released over 48 h. In contrast, under oxidative conditions mimicking the disease microenvironment, more than 90% of the BDNF is released within 24 h, demonstrating a ROS-triggered burst release behavior. These findings confirm that the hydrogel system can serve as an effective depot for delivering neurotrophic factors in a spatiotemporally controlled manner, releasing therapeutics selectively in disease-relevant regions where oxidative stress is present. Such responsiveness is particularly advantageous for minimizing systemic exposure, reducing side effects, and enhancing local therapeutic efficacy in the treatment of AD.

As shown in Figure 5, H_2O_2 exposure caused a dramatic increase in ROS production—approximately 3.5-fold higher than the baseline level observed in control cells. This elevation reflects substantial oxidative stress, which is known to compromise cellular viability and function. However, when the ROS-responsive hydrogel was co-administered, the intracellular ROS level was significantly attenuated, reduced to nearly 1.2-fold of the control, indicating that the hydrogel effectively neutralized excess ROS. The ROS-scavenging ability is attributed to the inclusion of antioxidant functional groups within the hydrogel matrix, such as thioether or phenylboronic ester moieties, which can react with H_2O_2 and other ROS species through oxidation-triggered chemical transformations. This redox-reactive behavior not only protects the cells from oxidative injury but also contributes to hydrogel degradation and subsequent drug release in a feedback-controlled manner. These results demonstrate that the hydrogel system is not only biocompatible but also actively mitigates oxidative stress *in vitro*, highlighting its dual functionality as both a drug carrier and a protective matrix in neurodegenerative disease environments.

In addition, we found that the concentration of the drug in the hippocampal region was significantly higher than that in the cortex, striatum and thalamus after injection, suggesting that the hydrogel system constructed in this study has good local enrichment ability and brain region targeting. Previous studies have demonstrated that stereotactic intracerebral injection of hydrogels is a safe and feasible approach; for example, silk fibroin-based hydrogels enabled effective *in situ* gelation and neuroprotection in a brain hemorrhage model [31]. Additionally, ECM hydrogels derived from urinary bladder matrix showed concentration-dependent gelation and excellent tissue permeation in stroke models, supporting the translational potential of injectable materials for central nervous system applications [32]. Our findings further confirm the *in vivo* distribution characteristics and targeted release advantage of the ROS-responsive hydrogel, providing a foundation for its development as an injectable therapeutic platform for AD.

While our research is focused on developing a "smart" hydrogel drug delivery system that responds to changes in ROS levels in the brain, it is used to achieve localized and precise release of BDNF to improve the therapeutic efficacy of AD. However, there are some research limitations. First, for example, the main goal of this study was drug delivery, and the hydrogel design focused on injectability and ROS responsiveness rather than as a brain tissue scaffold material. Therefore, the rheological evaluation was only used to confirm its structural stability and flexibility under physiological conditions, and its match with the elastic modulus of brain tissue was not further explored. Subsequent studies could introduce more detailed tissue matching analysis and optimize the hydrogel structure based on the biomechanical parameters of brain parenchyma to enhance its tissue integration ability for long-term application in the brain. In addition, the current experiments used a fixed BDNF concentration (100 ng/mL) to achieve faster release in a ROS environment, which has shown some neuroprotective effects but has not yet clarified its optimal loading interval and the biological advantages of a sustained slow-release strategy. In the future, we will carry out the loading efficiency test under different initial concentrations and verify whether long-term low-dose BDNF release is more helpful for nerve repair and synaptic remodeling in combination with animal models. Finally, although hydrogels achieved effective release in the *in vitro* setting, no dynamic tracking or functional validation of whether BDNF remained active in the hydrogel environment was performed. For this reason, we will further introduce the assay of BDNF pathway-related proteins to assess the functional activation effect of the releases on neuronal cells at different time points, thus verifying the retention of activity.

5. Conclusion

In this study, we developed a BDNF-loaded hydrogel system with ROS-responsive properties, capable of achieving localized and controlled release in the oxidative stress-rich brain microenvironment of AD. *In vivo* injection experiments demonstrated significant accumulation of the hydrogel in the hippocampal region, markedly enhancing local BDNF expression. Further investigations confirmed that the system could reduce ROS levels, alleviate inflammatory responses, and promote neuronal survival and repair. Compared with traditional drug delivery methods, this strategy offers enhanced targeting and biological responsiveness, with excellent biocompatibility and translational potential. This hydrogel platform holds promise as a novel therapeutic approach for AD and other neurodegenerative disorders.

References

1. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement.*, 20(5), 2024, 3708–3821.
2. CUMMINGS, J., ZHOU, Y., LEE, G., ZHONG, K., FONSECA, J., et al., Alzheimer's disease drug development pipeline: 2023. *Alzheimers Dement.-Transl. Res. Clin. Interv.*, 9(2), 2023, e12385.

3. JACK JR, C. R., ANDREWS, J. S., BEACH, T. G., BURACCHIO, T., DUNN, B. et al., Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement.*, 20(8), 2024, 5143–5169.
4. DEPP, C., SUN, T., SASMITA, A. O., SPIETH, L., BERGHOFF, S. A., et al., Myelin dysfunction drives amyloid-β deposition in models of Alzheimer's disease. *Nature*, 618(7964), 2023, 349–357. https://doi.org/10.1038/s41586-023-06120-6.
5. HANSSON, O., BLENNOW, K., ZETTERBERG, H., DAGE, J., Blood biomarkers for Alzheimer's disease in clinical practice and trials. *Nat. Aging*, 3(5), 2023, 506–519. https://doi.org/10.1038/s43587-023-00403-3.
6. HASSAN, H. M., ELNAGAR, M. R., ABDELRAZIK, E., MAHDI, M. R., HAMZA, E., et al., Neuroprotective effect of naringin against cerebellar changes in Alzheimer's disease through modulation of autophagy, oxidative stress and tau expression: an experimental study. *Front. Neuroanat.*, 16, 2022, 1012422. https://doi.org/10.3389/fnana.2022.1012422.
7. JORFI, M., MAASER-HECKER, A., TANZI, R. E., The neuroimmune axis of Alzheimer's disease. *Genome Med.*, 15(1), 2023, 6. https://doi.org/10.1186/s13073-023-01155-w.
8. JALIL, S., ALGHANEM, S. M. S., AL-HUQAIL, A. A., NAZIR, M. M., ZULFIQAR, F., et al., Zinc oxide nanoparticles mitigated the arsenic induced oxidative stress through modulation of physio-biochemical aspects and nutritional ions homeostasis in rice (*Oryza sativa* L.). *Chemosphere*, 338, 2023, 139566. https://doi.org/10.1016/j.chemosphere.2023.140622.
9. ZHU, S., ZHAO, B., LI, M., WANG, H., ZHU, J., et al., Microenvironment responsive nanocomposite hydrogel with NIR photothermal therapy, vascularization and anti-inflammation for diabetic infected wound healing. *Bioact. Mater.*, 26(12), 2023, 306–320. https://doi.org/10.1016/j.bioactmat.2023.03.005.
10. JANELIDZE, S., BALI, D., ASHTON, N. J., BARTHELEMY, N. R., VANBRABANT, J., et al., Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease. *Brain*, 146(4), 2023, 1592–1601. https://doi.org/10.1093/brain/awac333.
11. LEE, W. H., LEE, C. W., CHA, G. D., LEE, B.-H., JEONG, J. H., et al., Floatable photocatalytic hydrogel nanocomposites for large-scale solar hydrogen production. *Nat. Nanotechnol.*, 18(7), 2023, 754–762. https://doi.org/10.1038/s41565-023-01385-4.
12. LU, Y., YANG, G., WANG, S., ZHANG, Y., JIAN, Y., et al., Stretchable graphene-hydrogel interfaces for wearable and implantable bioelectronics. *Nat. Electron.*, 7(1), 2023, 51–65. https://doi.org/10.1038/s41928-023-01091-y.
13. WANG, Y., LI, Q., HONG, H., YANG, S., ZHANG, R., et al., Lean-water hydrogel electrolyte for zinc ion batteries. *Nat. Commun.*, 14(1), 2023, 3890. https://doi.org/10.1038/s41467-023-39634-8.
14. HU, L., CHEE, P. L., SUGIARTO, S., YU, Y., SHI, C., et al., Hydrogel-based flexible electronics. *Adv. Mater.*, 35(14), 2023, e2205326.
15. MARTINI, D., MARINO, M., VENTURI, S., TUCCI, M., KLIMIS-ZACAS, D., et al., Blueberries and their bioactives in the modulation of oxidative stress, inflammation and cardio/vascular function markers: a systematic review of human intervention studies. *J. Nutr. Biochem.*, 111(S1), 2023, 109154. https://doi.org/10.1016/j.jnutbio.2022.109154.
16. QIAO, L., LIANG, Y., CHEN, J., HUANG, Y., ALSAREII, S. A., et al., Antibacterial conductive self-healing hydrogel wound dressing with dual dynamic bonds promotes infected wound healing. *Bioact. Mater.*, 30(19), 2023, 129–141. https://doi.org/10.1016/j.bioactmat.2023.07.015.

17. ZHANG, H., ZHANG, D., WANG, Z., XI, G., MAO, R., et al., Ultrastretchable, self-healing conductive hydrogel-based triboelectric nanogenerators for human-computer interaction. *ACS Appl. Mater. Interf.*, 15(4), 2023, 5128–5138.
18. ZHANG, Y., CHEN, H., LI, R., STERLING, K., SONG, W., Amyloid β-based therapy for Alzheimer's disease: challenges, successes and future. *Signal Transduct. Targeted Ther.*, 8(1), 2023, 248. https://doi.org/10.1038/s41392-023-01484-7.
19. ZHOU, T., YUK, H., HU, F., WU, J., TIAN, F., et al., 3D printable high-performance conducting polymer hydrogel for all-hydrogel bioelectronic interfaces. *Nat. Mater.*, 22(7), 2023, 895–902. https://doi.org/10.1038/s41563-023-01569-2.
20. CLEMENTI, M. E., PIZZOFERRATO, M., BIANCHETTI, G., BRANCATO, A., SAMPAOLESE, B., et al., Cytoprotective effect of idebenone through modulation of the intrinsic mitochondrial pathway of apoptosis in human retinal pigment epithelial cells exposed to oxidative stress induced by hydrogen peroxide. *Biomedicines*, 10(2), 2022, 503. https://doi.org/10.3390/biomedicines10020503.
21. CHEN, Y., WANG, X., TAO, S., WANG, Q., MA, P. -Q., et al., Research advances in smart responsive-hydrogel dressings with potential clinical diabetic wound healing properties. *Military Med. Res.*, 10(1), 2023, 37. https://doi.org/10.1186/s40779-023-00473-9.
22. MIN, D. K., KIM, Y. E., KIM, M. K., CHOI, S. W., PARK, N., et al., Orally administrated inflamed colon-targeted nanotherapeutics for inflammatory bowel disease treatment by oxidative stress level modulation in colitis. *ACS Nano*, 17(23), 2023, 24404–24416. https://doi.org/10.1021/acsnano.3c11089.
23. ABOU EL-YAZIED, A., IBRAHIM, M. F. M., IBRAHIM, M. A. R., NASEF, I. N., AL-QAHTANI, S. M., et al., Melatonin mitigates drought induced oxidative stress in potato plants through modulation of osmolytes, sugar metabolism, ABA homeostasis and antioxidant enzymes. *Plants*, 11(9), 2022, 1151. https://doi.org/10.3390/plants11091151.
24. ALORABI, M., CAVALU, S., AL-KURAISHY, H. M., AL-GAREEB, A. I., MOSTAFA-HEDEAB, G., et al., Pentoxifylline and berberine mitigate diclofenac-induced acute nephrotoxicity in male rats via modulation of inflammation and oxidative stress. *Biomed. Pharmacother.*, 152(3), 2022, 113225. https://doi.org/10.1016/j.biopha.2022.113225.
25. QI, X., CAI, E., XIANG, Y., ZHANG, C., GE, X., et al., An Immunomodulatory hydrogel by hyperthermia-assisted self-cascade glucose depletion and ROS scavenging for diabetic foot ulcer wound therapeutics. *Adv. Mater.*, 35(48), 2023, e2306632. https://doi.org/10.1002/adma.202306632.
26. SHAO, Z., YIN, T., JIANG, J., HE, Y., XIANG, T., et al., Wound microenvironment self-adaptive hydrogel with efficient angiogenesis for promoting diabetic wound healing. *Bioact. Mater.*, 20(5), 2023, 561–573. https://doi.org/10.1016/j.bioactmat.2022.06.018.
27. QIU, Y., ZENG, Y., ZHANG, C., LV, X., LING, Y., et al., A ROS-responsive loaded desferoxamine (DFO) hydrogel system for traumatic brain injury therapy. *Biomed. Mater.*, 19(2), 2024, 025016. https://doi.org/10.1088/1748-605x/ad1dfd.
28. CAO, J., ZHANG, X., GUO, J., WU, J., LIN, L., et al., An engineering-reinforced extracellular vesicle-integrated hydrogel with an ROS-responsive release pattern mitigates spinal cord injury. *Sci. Adv.*, 11(14), 2025, eads3398. https://doi.org/10.1126/sciadv.ads3398.
29. SUN, H., XU, J., WANG, Y., SHEN, S., XU, X., et al., Bone microenvironment regulative hydrogels with ROS scavenging and prolonged oxygen-generating for enhancing bone repair. *Bioact. Mater.*, 24(2), 2023, 477–496. https://doi.org/10.1016/j.bioactmat.2022.12.021.
30. GUO, W., HU, C., WANG, Y., ZHANG, W., ZHANG, S., et al., NO-releasing double-crosslinked responsive hydrogels accelerate the treatment and repair of ischemic stroke. *Acta Pharm. Sin. B*, 15(2), 2025, 1112–1125. https://doi.org/10.1016/j.apsb.2025.01.005.

31. ZHANG, J., LI, S., YANG, Z., LIU, C., CHEN, X., et al., Implantation of injectable SF hydrogel with sustained hydrogen sulfide delivery reduces neuronal pyroptosis and enhances functional recovery after severe intracerebral hemorrhage. *Biomater. Adv.*, 135(4), 2022, 212743. https://doi.org/10.1016/j.bioadv.2022.212743.
32. MASSENSINI, A. R., GHUMAN, H., SALDIN, L. T., MEDBERRY, C. J., KEANE, T. J., et al., Concentration-dependent rheological properties of ECM hydrogel for intracerebral delivery to a stroke cavity. *Acta Biomater.*, 27, 2015, 116–130. https://doi.org/10.1016/j.actbio.2015.08.040.

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