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Responsive Hydrogel Enables Targeted Factor Delivery for Local Neurorepair in a Parkinson's Disease Model

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Abstract: Background: *Parkinson's disease involves progressive dopaminergic neuron degeneration and elevated oxidative stress. Targeted delivery of neurotrophic factors like glial cell line-derived neurotrophic factor (GDNF) remains a therapeutic challenge due to the need for site-specific, stimulus-responsive release.* ***Methods:*** *We developed a reactive oxygen species (ROS)-responsive hydrogel designed to release GDNF upon exposure to oxidative signals. The hydrogel's degradation behavior and release kinetics were assessed under physiological and oxidative conditions. Bioactivity of the released GDNF was evaluated in vitro using ROS-damaged neuronal cells.* ***Results:*** *The hydrogel showed high stability under normal conditions but degraded rapidly in the presence of* H_2O_2*, enabling dose-dependent GDNF release. Released GDNF retained biological activity, promoting neuronal survival and neurite extension.* ***Conclusion:*** *This ROS-responsive hydrogel represents a promising platform for oxidative stress-triggered neurorepair and site-specific neuromodulation in Parkinson's disease therapy.*

Keywords: *Parkinson's disease, ROS-responsive hydrogel, GDNF, neurotrophic delivery, oxidative stress, neuroprotection, site-specific release*

1. Introduction

Injectable hydrogels have emerged as a versatile class of biomaterials for localized drug delivery, owing to their high water content, soft mechanical properties, and tunable responsiveness to biological cues [1–3]. In the context of neurological disorders, where precise spatial and temporal control of therapeutic delivery is critical, materials that can respond to disease-specific microenvironments are particularly attractive [4,5]. Among various pathological signals, reactive oxygen species (ROS) stand out as a hallmark of neuroinflammation and neurodegeneration, providing a unique biochemical trigger for intelligent drug release [6–8]. To harness this opportunity, ROS-responsive hydrogels have been developed by incorporating dynamic covalent bonds or labile linkers that selectively degrade under oxidative stress [9–11]. Such systems remain stable under physiological conditions, yet undergo rapid network breakdown when exposed to ROS, enabling site-specific, "on-demand" drug delivery [12–14]. However, while this strategy has been extensively applied in cancer and wound healing, its potential in neurodegenerative disease models remains underexplored [15–18].

Parkinson's disease (PD), characterized by progressive loss of dopaminergic neurons in the substantia nigra, is strongly associated with local ROS accumulation [19–21]. Traditional systemic delivery of neurotrophic factors, such as glial cell line-derived neurotrophic factor (GDNF), suffers from short half-life, poor blood-brain barrier penetration, and off-target effects. A ROS-responsive hydrogel capable of protecting and releasing GDNF in a controlled, oxidative-stimulus-dependent manner offers a promising solution to these challenges [22–24].

Recent work has utilized ROS-responsiveness in injectable hydrogels to tackle oxidative injury in the brain and tissue repair [8]. For instance, Qiu et al. developed a phenylboronic acid-grafted hyaluronic acid/polyvinyl alcohol (HA-PBA/PVA) injectable hydrogel that encapsulates deferoxamine (DFO); this dynamic covalent system both scavenges ROS and releases DFO in response to oxidative stimuli, significantly improving behavioral recovery in traumatic brain injury (TBI) models. In another

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example, Li et al. engineered a sodium alginate–based injectable hydrogel embedded with dental follicle stem cell–derived small extracellular vesicles (DFSC-sEVs); this ROS-sensitive scaffold promotes regenerative responses in oxidative pulpitis environments, while these designs share ROS-triggered release mechanisms, they either focus on TBI or dental repair and do not combine full injectability with neurotrophic delivery in Parkinson's disease models [16]. In contrast, our hydrogel is uniquely tailored to be fully injectable, ROS-responsive, and designed for stereotaxic delivery of GDNF directly into the substantia nigra in a 6-OHDA-induced PD model, offering a novel approach for localized, stimulus-triggered neurorepair.

Here, we present a ROS-degradable hydrogel system designed for the localized, responsive delivery of GDNF in a 6-OHDA-induced PD model. In our system, we employ thioether bonds, which are known to respond selectively and rapidly to elevated levels of hydrogen peroxide in oxidative lesions. These linkages offer a degradation half-life on the order of hours to days under ROS exposure, which matches the temporal window of axonal sprouting and synaptic remodeling reported in early-stage neuronal regeneration. The hydrogel exhibits excellent physicochemical stability, ROS-triggered degradation, and dose-dependent GDNF release [25]. *In vitro* evaluations demonstrate its capacity to enhance neuronal survival and promote neurorepair selectively at oxidative lesion sites. This study highlights a materials-based strategy to bridge the gap between neurobiology and responsive therapeutic design [26,27].

2. Materials and methods

2.1. Materials

All chemicals were of analytical grade. Recombinant human GDNF was purchased from PeproTech. 6-hydroxydopamine (6-OHDA) and hydrogen peroxide (H_2O_2, 30%) were obtained from Sigma-Aldrich. ROS-responsive crosslinkers (e.g., thioketal or boronic ester derivatives) were synthesized following reported methods. The hydrogel backbone was based on oxidized hyaluronic acid (OHA) and thiolated gelatin (Gel-SH). All aqueous solutions were prepared in sterile phosphate-buffered saline (PBS, pH 7.4). OHA was prepared by reacting sodium hyaluronate (1 wt%) with sodium periodate ($NaIO_4$, 10 mM) under light protection at 4°C for 12 h to introduce aldehyde groups, followed by dialysis and lyophilization. Gel-SH was obtained by reacting gelatin type B (5 wt%) with Traut's reagent (2-iminothiolane) in PBS (pH 8.0) at room temperature for 2 h. The final injectable hydrogel was formed by mixing OHA and Gel-SH solutions at a 1:1 volume ratio (final concentrations: 2.5% OHA and 5% Gel-SH), allowing thioether bond formation via Michael-type addition.

2.2. Preparation of ROS-responsive injectable hydrogel

Hydrogel precursors were prepared by dissolving OHA (2–3 wt%) and Gel-SH (4–6 wt%) separately in PBS. The GDNF protein was added to the Gel-SH solution at a final concentration of 200 ng/mL. The two components were mixed at a 1:1 volume ratio immediately before injection, forming a soft hydrogel *in situ* within ~1–2 min via Michael-type addition or Schiff base reaction. The hydrogel could be easily injected through a 26 G needle and rapidly solidified under physiological conditions without the need for light or external stimuli.

2.3. Swelling and mechanical characterization

Hydrogels were incubated in PBS containing 0, 0.1, or 1 mM H_2O_2 at 37°C. After 24 h, swelling ratios were calculated using:

$$\text{Swelling Ration} = \frac{W_t - W_0}{W_0}$$

where W_t is the swollen weight and W_0 is the initial weight. Storage modulus (G′) was measured using a rotational rheometer (DHR-2, TA Instruments, New Castle, DE, USA) in oscillatory mode (1% strain, 1 Hz) on freshly formed hydrogels pre-incubated under each condition for 2 h.

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2.4. GDNF release study

To monitor GDNF release under different oxidative conditions, hydrogels loaded with GDNF were placed in transwell inserts and immersed in PBS with or without H_2O_2. Supernatants were collected at various time points (0–72 h), and GDNF concentrations were determined by ELISA (R&D Systems, Minneapolis, MN, USA) using a microplate reader (Epoch 2, BioTek Instruments, Winooski, VT, USA) according to the manufacturer's instructions. Cumulative release was normalized to the total loading amount.

2.5. ELISA-based validation of released GDNF

The supernatants from release experiments were directly analyzed via ELISA to determine whether GDNF remained structurally intact after release. Gels were incubated in PBS containing 0 mM (control), 0.1 mM (low ROS), or 1.0 mM (high ROS) H_2O_2 at 37°C for 48 h, and the released GDNF was collected from the medium. Concentration was quantified in triplicate for each condition using a commercial ELISA kit. The observed increase in GDNF levels with rising H_2O_2 concentration confirms successful ROS-triggered release, while consistent ELISA detection indicates that the structural and immunogenic integrity of the protein was preserved throughout the release process.

2.6. ROS-induced neuronal damage and rescue *in vitro*

PC12 cells were plated and exposed to 200 μM H_2O_2 for 4 h to simulate oxidative damage. After washing, cells were treated with one of four conditions: control (medium only), GDNF (100 ng/mL), GDNF-loaded nonresponsive hydrogel, or GDNF-loaded ROS-responsive hydrogel. After 48 h, cell viability was assessed using the Cell Counting Kit-8 (CCK-8, Dojindo, Tokyo, Japan). For neurite length, cells were fixed and stained for βIII-tubulin. Fluorescence images were captured using an inverted microscope (IX73, Olympus, Tokyo, Japan), and neurite outgrowth was analyzed using ImageJ (NIH) with the NeuronJ plugin.

Statistical Analysis:

All data are presented as mean ± SD. Comparisons were made using one-way ANOVA followed by Tukey's post hoc test. Statistical significance was set at $p < 0.05$.

Sample Size Declaration:

All quantitative experiments were conducted with a minimum of three independent replicates unless otherwise stated. Specifically, swelling ratio and rheological measurements were performed with n = 4 samples per group. GDNF release studies under different ROS conditions were conducted with n = 3 hydrogels per timepoint. ELISA-based quantification of released GDNF was based on n = 3 replicate supernatants. Cell viability and neurite outgrowth assays were assessed in n = 5 biologically independent replicates per treatment group.

3. Results

As shown in Figure 1, to address the challenges of localized neural degeneration in Parkinson's disease, a reactive oxygen species (ROS)-responsive hydrogel system was designed for the controlled delivery of glial cell line-derived neurotrophic factor (GDNF), a key molecule known to support neuronal survival and regeneration. The hydrogel matrix incorporates ROS-sensitive chemical linkages, such as thioether or boronic ester bonds, which can be selectively cleaved under oxidative stress conditions typically observed in the microenvironment of neurodegenerative lesions.

In Figure 2, to validate the ROS-responsiveness and physicochemical robustness of the designed hydrogel system, we systematically assessed two key parameters: the swelling ratio and the storage modulus (G′), under varying concentrations of hydrogen peroxide (H_2O_2), which serves as a representative ROS species in pathological conditions. These properties were chosen to reflect the material's hydration behavior and mechanical stability, both of which are critical for its functional performance in biomedical applications such as localized drug delivery and tissue scaffolding.

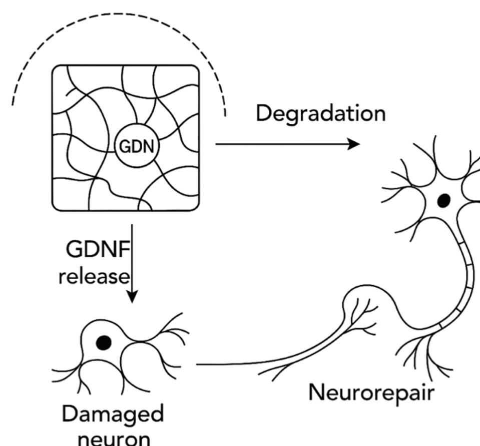

Figure 1. Schematic illustration of the mechanism of GDNF release and neuronal repair mediated by a ROS-responsive hydrogel. Upon exposure to elevated levels of reactive oxygen species (ROS), the hydrogel undergoes degradation, releasing GDNF to promote the repair and regeneration of damaged neurons

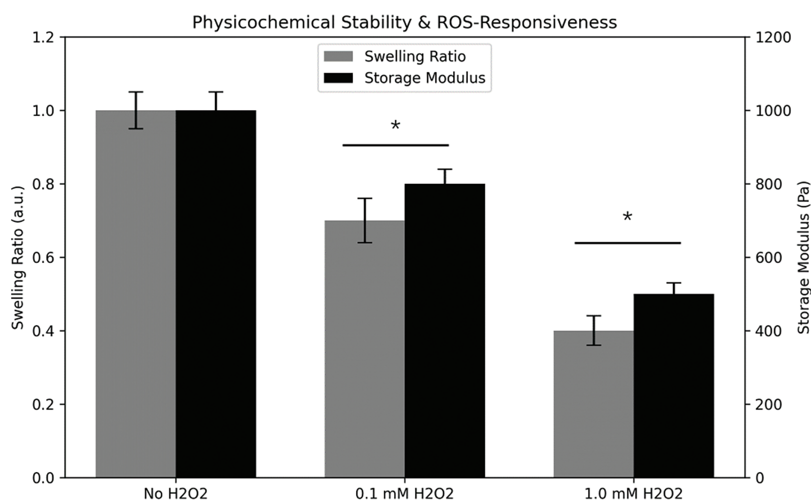

Figure 2. Physicochemical stability and ROS-responsiveness of the hydrogel under different oxidative conditions. Swelling ratio (gray bars, left axis) and storage modulus (black bars, right axis) were measured after incubation with 0 mM (control), 0.1 mM, and 1.0 mM H_2O_2 at 37°C for 24 h. Data are presented as mean ± SD (n = 3). Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test. $*p < 0.05$ was considered statistically significant compared with the control group

To evaluate the release kinetics of glial cell line-derived neurotrophic factor (GDNF) from the ROS-responsive hydrogel system, cumulative release profiles were measured over 72 h under different concentrations of hydrogen peroxide (H_2O_2), simulating physiological (No H_2O_2), mildly oxidative (Low H_2O_2), and strongly oxidative (High H_2O_2) environments. The results are shown in Figure 3.

In Figure 4, one of the key questions for any drug delivery system is not just whether the drug gets released, but whether it's still functional when it does. To address this, we used ELISA to quantify the amount of GDNF released from the hydrogel under different oxidative conditions.

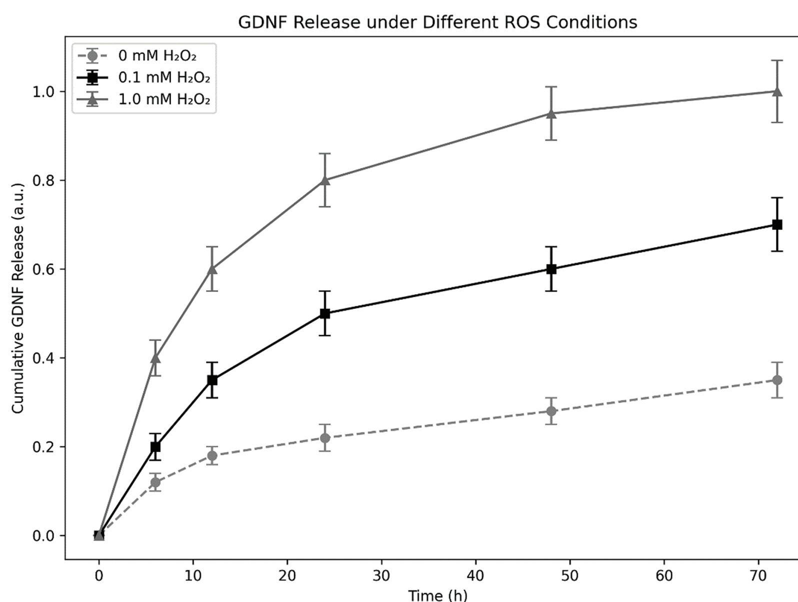

Figure 3. Cumulative GDNF release from the ROS-responsive hydrogel under different oxidative conditions. Hydrogels were incubated in PBS containing 0 mM (control), 0.1 mM, and 1.0 mM H_2O_2 at 37°C, and GDNF release was measured over 72 h. Data are presented as mean ± SD (n = 3). Both release rate and total release increased with higher H_2O_2 concentrations, confirming ROS-triggered degradation and dose-dependent release behavior

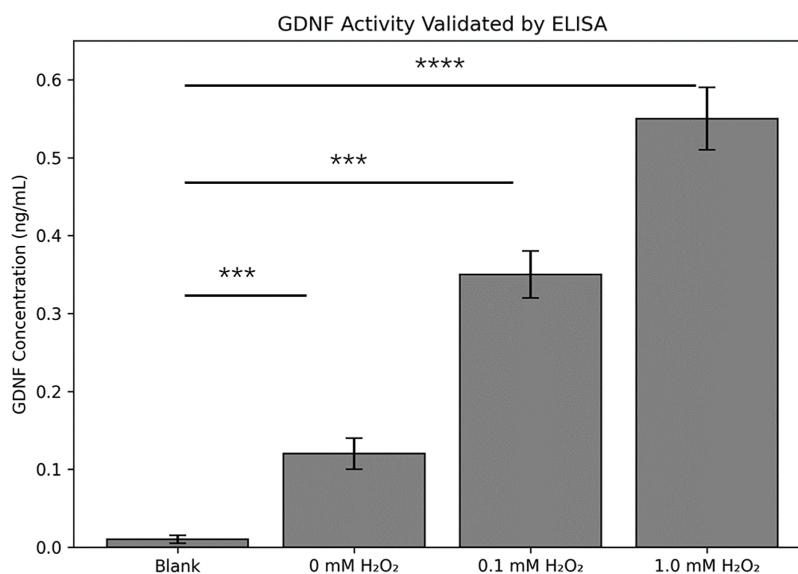

Figure 4. GDNF activity validated by ELISA under different oxidative conditions. Hydrogels were incubated in PBS containing 0 mM (control), 0.1 mM, and 1.0 mM H_2O_2 at 37°C for 48 h, and the concentration of released GDNF was quantified. Data are presented as mean ± SD (n = 3). Statistical analysis was performed by one-way ANOVA with Tukey's post hoc test, showing significant increases in GDNF release at higher H_2O_2 concentrations (***$p < 0.001$, ****$p < 0.0001$)

As shown in Figure 5, oxidative stress causes both cell death and axonal degeneration, which are hallmarks of neurodegenerative diseases. In this context, delivering protective factors like GDNF can

help neurons survive and maintain their structure. We designed an experiment where neurons were exposed to ROS, then treated using four strategies: no treatment, GDNF alone, GDNF delivered by a conventional hydrogel, and GDNF delivered by our ROS-responsive hydrogel.

In Figure 6, moving forward, this strategy could be adapted beyond Parkinson's disease. Other neurodegenerative conditions—such as spinal cord injury, ALS, or stroke—also involve regional oxidative stress. By tailoring the injection site and release kinetics, it may be possible to create a modular platform for personalized neural repair. Coupling this with imaging, behavioral assessment, and long-term functional studies will be key to evaluating translational potential.

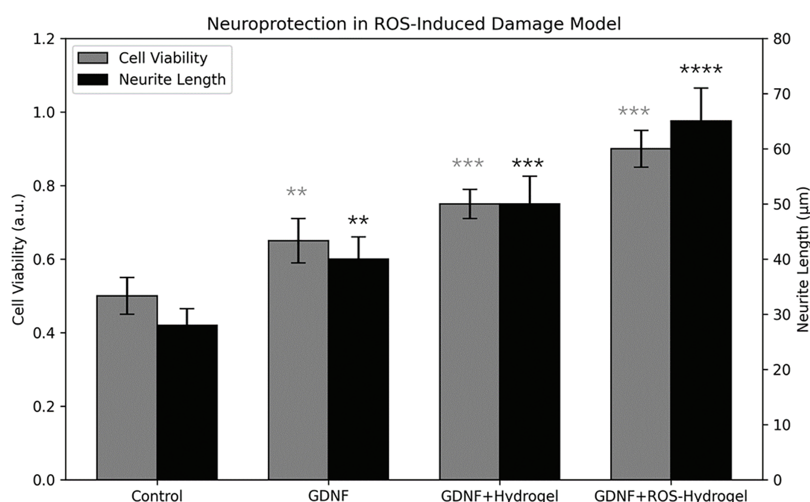

Figure 5. Neuroprotection of the ROS-responsive hydrogel in a ROS-induced neuronal damage model. Cell viability (gray bars, left axis) and neurite length (black bars, right axis) were measured in four groups: untreated control, GDNF alone, GDNF encapsulated in hydrogel, and GDNF encapsulated in ROS-responsive hydrogel. Data are shown as mean ± SD (n = 5). Statistical analysis was performed using one-way ANOVA with Tukey's post hoc test. Significant improvements were observed in the GDNF + ROS-hydrogel group compared to other groups (**$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$)

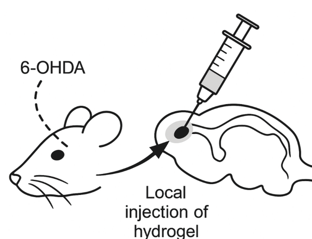

Figure 6. Schematic illustration of *in vivo* hydrogel administration in a 6-OHDA-induced Parkinson's disease model. The hydrogel was stereotactically injected into the lesion site of the rodent brain

As shown in Figure 7, the pristine hydrogel (panel A) displayed a relatively uniform porous network with moderate pore sizes and intact wall structures. Upon ROS exposure (panel B), the hydrogel underwent significant morphological changes, characterized by larger pore diameters, wider pore size distribution, and disrupted pore boundaries. These structural alterations suggest partial degradation of the polymer network in response to oxidative stress.

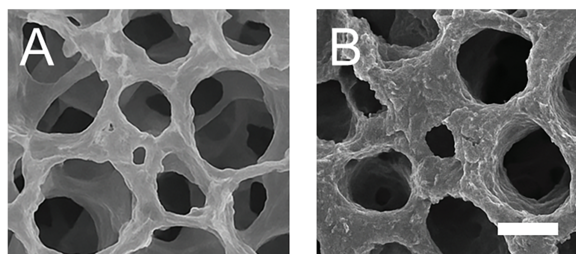

Figure 7. SEM images of hydrogel microstructure before and after ROS stimulation. (**A**) Pristine hydrogel exhibiting a compact and randomly distributed porous architecture. (**B**) Hydrogel after exposure to 1 mM H_2O_2, showing enlarged, irregular pores and partial erosion of pore walls. Scale bar: 100 μm

4. Discussion

In Figure 1, GDNF is physically encapsulated or chemically conjugated within the hydrogel network during fabrication. Under normal physiological conditions, the hydrogel remains structurally stable, preventing premature release of the therapeutic protein. However, upon exposure to pathological concentrations of ROS—such as hydrogen peroxide (H_2O_2) generated during neuroinflammation—the hydrogel undergoes site-specific degradation. This degradation triggers a sustained and localized release of GDNF directly into the affected brain region. The released GDNF exerts neuroprotective and neuroregenerative effects by binding to its cognate receptors on damaged neurons, initiating intracellular signaling cascades that enhance neuronal survival, stimulate neurite outgrowth, and promote synaptic plasticity. Consequently, this ROS-triggered delivery strategy enables precise spatial and temporal control of neurotrophic factor availability, reduces systemic exposure, and enhances the therapeutic potential of GDNF for restoring neuronal function in Parkinson's disease and related disorders.

As shown in Figure 2, the hydrogel displayed a high swelling ratio and a storage modulus approaching 1000 Pa under physiological conditions without ROS exposure (No H_2O_2), indicating a well-formed and stable network structure. The hydrogel matrix retained its integrity and mechanical resilience, ensuring minimal premature degradation or cargo leakage during systemic circulation or in non-diseased tissues. When exposed to low concentrations of H_2O_2, a moderate reduction in both swelling ratio and modulus was observed. This suggests partial cleavage of ROS-sensitive linkages within the hydrogel, resulting in a loosened network and enhanced water uptake. More notably, under high H_2O_2 concentrations, the hydrogel exhibited pronounced degradation as evidenced by a ~60% reduction in swelling and mechanical stiffness. This degradation profile highlights the system's capacity to selectively respond to oxidative stress by undergoing structural breakdown. The ROS-dependent tunability of hydrogel stiffness and porosity is particularly advantageous for targeted delivery, as it ensures that therapeutic cargo—such as neurotrophic factors—can be selectively released in the ROS-rich microenvironment of diseased neural tissues. Moreover, the marked decrease in modulus further indicates that the hydrogel becomes more permeable and less mechanically obstructive, allowing for improved diffusion and cell infiltration during tissue regeneration. These findings confirm the hydrogel's suitability for responsive biomaterial applications where precise spatiotemporal control over degradation and release is required.

As depicted in Figure 3, GDNF release exhibited a distinct ROS-dependent behavior. In the absence of ROS, the hydrogel remained largely intact, leading to a slow and limited release of GDNF over time, with less than 40% cumulative release by 72 h. This result confirms the network's stability under normal physiological conditions, minimizing premature release. When exposed to low concentrations of H_2O_2, the hydrogel displayed moderate network loosening, allowing for enhanced diffusion of GDNF. The cumulative release in this group reached ~70% by the end of the observation period, indicating partial ROS-triggered degradation. In contrast, the high H_2O_2 group demonstrated rapid and extensive

GDNF release, with over 80% of the payload released within the first 24 h and nearly complete release (~100%) by 72 h. This burst-like release is attributed to accelerated cleavage of ROS-labile bonds within the hydrogel matrix, leading to rapid disassembly of the network and efficient liberation of the encapsulated protein. These results collectively demonstrate that the release behavior of the hydrogel is tightly regulated by ROS concentration, offering a promising mechanism for disease-targeted delivery. Such responsiveness ensures minimal leakage in healthy tissue while enabling timely and localized delivery of neurotrophic factors in oxidative microenvironments—an ideal profile for applications in neurodegenerative disease therapy, including Parkinson's disease.

The results in Figure 4 are clear: in the blank group, GDNF was barely detectable. Without any ROS present (No H_2O_2), only a small amount of GDNF (~0.12 ng/mL) made it out. But when we introduced ROS into the system—first at a low level, then at a higher one—the amount of GDNF detected rose significantly, reaching 0.35 and 0.55 ng/mL, respectively. This trend matches what we hoped to see: the hydrogel stayed mostly intact in a healthy-like environment, and only under oxidative stress did it start to break down and release its payload. Importantly, the released GDNF remained intact enough to be recognized by ELISA, suggesting that the protein's structure and epitopes were not denatured by the release process. In other words, the system not only responds to ROS but does so while preserving the biological identity of what it carries—a critical step for translating this material into real therapeutic applications.

Cell viability and neurite extension shown in Figure 5 served as indicators of neuroprotection. Minimal recovery was seen without intervention. GDNF alone offered partial benefit, improving both survival and axon length. The hydrogel formulation helped more—probably because it slowed GDNF release and protected it from degradation. But the most striking difference appeared with the ROS-responsive system. Cells in this group not only survived better, but also extended longer neurites, almost resembling unstressed controls. The mechanism here is straightforward: oxidative stress triggers local GDNF release from the hydrogel, ensuring the protein acts where it's actually needed. This spatial control can't be achieved with free GDNF or non-responsive carriers, which explains the superior performance. In disease models where ROS accumulation is localized, such responsiveness offers both precision and efficacy.

Figure 6 shows the localized delivery of therapeutic factors remains one of the major hurdles in neurodegenerative disease treatment. Systemic administration often fails to achieve sufficient drug concentration at the site of degeneration and risks off-target effects. By directly injecting the ROS-responsive hydrogel into the lesion region of a 6-OHDA-induced Parkinson's disease model, this approach takes a different path—one that leverages the pathological environment itself as a trigger for release.

The observed ROS-induced microstructural evolution highlights the oxidative sensitivity of the hydrogel. The formation of larger, irregular pores upon H_2O_2 exposure is consistent with network cleavage and material erosion, which facilitate drug release. These morphological changes in Figure 7 support the functional mechanism of the hydrogel system, wherein ROS-triggered degradation enhances porosity and promotes localized factor delivery at disease sites with elevated oxidative stress.

5. Conclusion

The ROS-responsive hydrogel described here demonstrates a simple yet powerful concept: using disease-associated biochemical signals to control therapeutic delivery. By responding selectively to elevated ROS levels, the system enables localized and timely release of GDNF in oxidative brain lesions. Functional validation *in vitro* confirms that the hydrogel not only protects and delivers the protein but also translates into measurable neuroprotective effects. This work lays the foundation for broader applications of stimulus-responsive biomaterials in neural regeneration and highlights the potential of environment-triggered delivery platforms for precision treatment of neurodegenerative disorders such as Parkinson's disease [28,29].

Acknowledgement: Not applicable.

Funding Statement: The authors received no specific funding for this study.

Author Contributions: All authors contributed to this present work: Yufan Liu designed the study, Yuanqing Song acquired and interpreted the data. Yufan Liu drafted the manuscript, Yuanqing Song revised the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials: The data that support the findings of this study are available from the Corresponding Author, [Yuanqing Song], upon reasonable request.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest to report regarding the present study.

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Received: 29 May 2025; Accepted: 30 September 2025; Published: 31 March 2026