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Innovations in Injectable Conductive Hydrogels for Neural Regeneration and Biointerface Compatibility

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INTRODUCTION & AIM

Background: The nervous system's restricted ability to regenerate represents a therapeutic gap in the treatment of neural injuries and degenerative disorders [1]. Conventional therapies, including pharmacological treatments, surgical interventions, electrical stimulation therapies, and neurorehabilitation, rarely lead to full recovery, especially in cases involving impaired neural signaling [2]. Injectable conductive hydrogels have become potential candidates for therapeutic applications in neural tissue engineering [2]. Hydrogels are ideal due to their biocompatibility, tunable mechanics, and injectability allowing minimally invasive delivery [3]. Their high-water content facilitates rapid nutrient diffusion while their electrical conductivity enhances neuronal signaling, and their mechanical properties allow for controllable drug release [3]. Hydrogels promote a compatible interface with existing neural tissue, enabling integration and supporting efficient interaction [3].

Gap: Despite recent advancements in injectable conductive hydrogels for neural tissue engineering, there remains limited understanding of the extent to which these injectable hydrogels can mimic the native neural microenvironment and sustain neural activity in vitro [4].

Aim: The aim of this manuscript is to investigate the potential of utilizing injectable conductive hydrogels as biomimetic materials that can support neural biointerface integration and facilitate neural tissue regeneration.

Expected Results

The proposed injectable conductive GelMA-based hydrogel is exhibited to demonstrate mechanical properties, porosity, and electrical conductivity similar to native neural tissue while maintaining structural stability after crosslinking. The hydrogel is expected to provide a biocompatible microenvironment that supports processes vital to cell proliferation and differentiation such as nutrient diffusion, cell adhesion, and cellular signaling.

Neural stem cells within the hydrogel are expected to demonstrate high cell viability and proliferation as determined by MITT assays. Immunostaining for β-III tubulin is expected to demonstrate successful neuronal differentiation, extensive neurite outgrowth, increased neurite branching, and formation of interconnected neuronal networks throughout the matrix. These features collectively indicate that the neural cells are viable and functionally interacting with the neuronal environment. Electrophysiological assessment using MEA recordings are expected to demonstrate spontaneous electrical activity, synchronized neuronal firing, and enhanced signal propagation. These findings demonstrate that not only differentiation was successful but also that the cells are viable. Collectively, these findings indicate that injectable conductive hydrogels have the potential to serve as biomimetic scaffolds that enhance neuronal viability, differentiation, and compatibility, in turn promoting functional neuronal regeneration.

Conclusion

Injectable conductive hydrogels represent a promising biomimetic platform for neural tissue engineering due to its biocompatibility, tunable mechanical properties, and electrical conductivity. Current studies performed to assess hydrogel properties have demonstrated successful neuronal survival, differentiation, neurite extension, and functional neural network formation [5]. Collectively, these underscore the potential to enhance neural regeneration and improve biointerface compatibility. Nevertheless, further in vivo studies and clinical translation are required to establish long-term safety, efficacy, and therapeutic potential of these hydrogels.

Clinical Significance

Neurological disorders, such as strokes and spinal cord injuries, represent a major therapeutic barrier in the field of medicine as mature neurons in the central nervous system have limited capacity for regeneration after injury [1]. Consequently, central nervous system injuries and disorders result in permanent functional deficits, highlighting the need for effective regenerative therapies [1]. Injectable conductive hydrogels demonstrate the potential to address this need in a minimally invasive manner to repair damaged neural tissue. This capacity carries significant clinical relevance, as it suggests that patients with spinal cord injuries, peripheral nerve injuries, traumatic injuries, stroke history, and neurodegenerative diseases could potentially benefit from regenerative therapeutic approaches. Moreover, their inherent biocompatibility can enhance the performance and stability of implantable neural devices, which in turn can improve their therapeutic efficacy.

METHOD

1. **Hydrogel fabrication:** Gelatin methacrylate (GelMA) is synthesized through methacrylation of gelatin and combined with conductive materials to form an injectable conductive precursor solution.
2. **Hydrogel formation and crosslinking:** The GelMA precursor solution that contains conductive nanomaterial and a photoinitiator is prepared under sterile conditions. The solution is injected into a mold and crosslinked using 365 nm UV to allow for the polymerization of methacrylate groups to form a three-dimensional hydrogel network.
3. **Physicochemical characterization:** The hydrogel network is evaluated under a series of tests to determine its mechanical properties, electrical conductivity, porosity, and structural rigidity.
4. **Cell encapsulation:** Neural stem cells are incorporated in the GelMA precursor solution before the crosslinking process occurs to mimic native neural architecture.
5. **In Vitro cell culture:** The hydrogels are cultured under standardized physiological conditions and cell survival and proliferation using colorimetric MTT assays.
6. **Neural differentiation and morphological analysis:** Immunostaining for β-III tubulin is used to confirm neuronal differentiation and to visualize neurite extension within the hydrogel matrix. The formation of neuronal networks is assessed to evaluate the structural organization and maturation of differentiated cells.
7. **Electrophysiological function testing:** A multielectrode array (MEA) system is used to analyze electrical activity generated by neural cells within the hydrogel matrix, specifically evaluating signal transmission, network synchronization, and functional connectivity.
8. **Statistical analysis:** Experimental data collected will undergo statistical analysis to evaluate validity of findings and determine significance of observed differences between experimental groups.

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