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Local immunomodulating AT1R-pathway blocker loaded reversibly thermoresponsive hydrogel for the treatment of peripheral neuropathy

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Purpose

Peripheral neuropathy refers to peripheral nervous system disorders with heterogeneous etiology, diverse pathology, and clinical manifestations like pain coming from inflammation and nerve degeneration. The impaired transition of pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages leads to chronic inflammation and lasting pain. Fibroblasts, producing a battery of cytokines and chemokines, direct macrophage phenotype and functions. The need for etiological therapy aimed at modifying the pathophysiological mechanisms engaging key cellular entities in inflammation and fibrosis is still unmet. Signaling pathways involving both macrophage and fibroblast are compelling targets for analgesia and type 1 angiotensin II (Ang II) receptor (AT1R) pathway involves Ang II, a pro-inflammatory peptide hormone that has a role in fibrosis and inflammation.

Our lab has previously shown that captopril-loaded hydrogel is effective in elevating mechanical sensitivity in a diabetic mouse model rapidly but for a short duration due to the faster release of drug. We propose a novel formulation of AT1-receptor antagonists (losartan) and ACE inhibitors (captopril) loaded into reversibly thermoresponsive hydrogel injected locally that can block AT1R pathway inhibiting macrophage and fibroblast pro-inflammatory activity and provide effective rapid and long-lasting analgesic activity. Optimized hydrogel with losartan which acts upstream and captopril which acts downstream of the AT1R pathway, will be complementary in suppressing inflammatory markers associated with peripheral nerve injury.

Methods

Mixed pluronic-based hydrogel formulation was optimized by implementing a 2-level 2-factor central composite design (CCD). Losartan and captopril were loaded into micelles first and then the micelles were dispersed into hydrogel.

Results

The design of experiment (DoE) results showed a correlation between viscosity and the concentration of pluronics in the hydrogel. The colloidal tests confirm stability, while the rheological tests demonstrate the viscoelastic and thermoresponsive properties of an injectable hydrogel. Both drug-free and drug-loaded hydrogels were found sterile and viable in macrophage cell lines, which were mandatory for the intended in-vivo and cell culture experiments. Losartan showed a very controlled slower release from the hydrogel compared to the captopril.

Conclusion

We have shown that AT1-receptor antagonists and ACE inhibitors can be loaded into reversibly thermoresponsive injectable hydrogel optimized implementing statistical experimental modeling with robust quality control.

Keywords: Peripheral neuropathy, AT1R pathway, hydrogel