pH-responsive Nanoparticles for Targeted Drug Delivery in Neonatal Hypoxic-Ischemic Brain Injury

Narayanamurthy, R[1], Waduthanthri KD[2], Yang, JL[2], Armstrong, EA[1], Yager, JY[1], Unsworth, LD[2]

[1]Department of Pediatrics, University of Alberta, Edmonton, [2] Department of Chemical and Materials Engineering, University of Alberta, Edmonton

Background

Therapeutic hypothermia is the only approved treatment against neonatal hypoxic-ischemic brain damage (HIBD), despite its limited effectiveness in offering neuroprotection.

Combining hypothermia with targeted drug delivery may help address this unmet clinical need and circumvent challenges associated with systemic drug administration.

Objectives

1. To design a drug delivery system using elastin-like polypeptides that can reversibly self-assemble into drug loaded-nanoparticles.
2. As the nanoparticles release drugs in a temperature- and pH-dependent manner, utilize brain hypothermia and the distinctively acidic site of brain injury to trigger drug release targeting the damaged region.

Methods

ELPs were synthesized using recursive directional ligation, expressed in *E.coli* and purified by inverse temperature cycling.

Dynamic light scattering and high-performance liquid chromatography were used to determine the optimal solution conditions for nanoparticle formation with drug encapsulation.

We designed a focal brain cooling chamber to effectuate selective brain hypothermia (Figure 1).

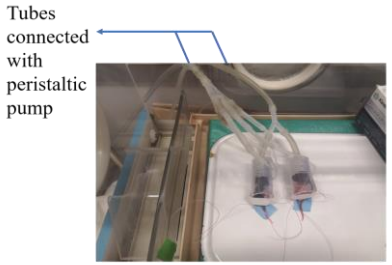

Figure 1. Long-Evans rats at PD7 inside the cooling chamber placed inside an incubator kept at 37°C.

Results

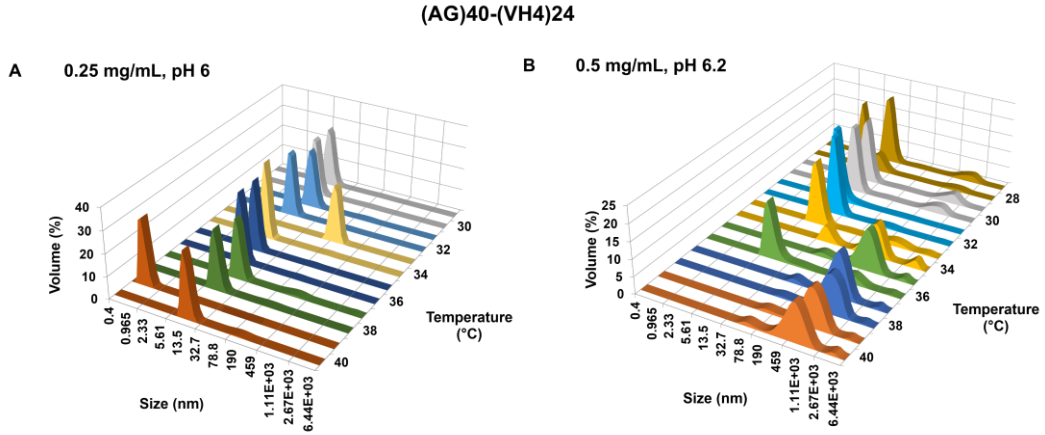

Figure 1. pH-induced disassembly of ELP at two concentrations encapsulating dexamethasone (DEX). The figure shows the volumetric distribution of nanoparticle size between 40°C and 28°C at pH 6 (A) and pH 6.2 (B).

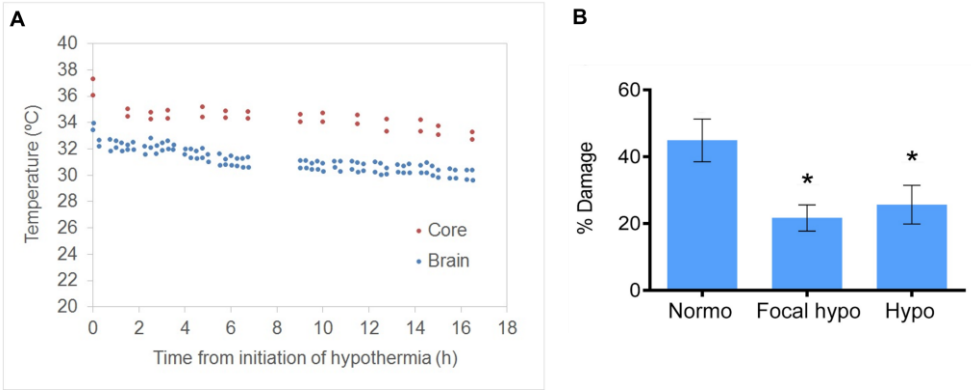

Figure 3. (A) Temperature profile of the rats over time. **(C)** Comparison of extent of damage (in percentage) in normothermic/HI, focal/HI and hypothermia/HI groups. Bars represent mean ± SD. *$p < 0.05$ by Kruskal-Wallis Test.

Results

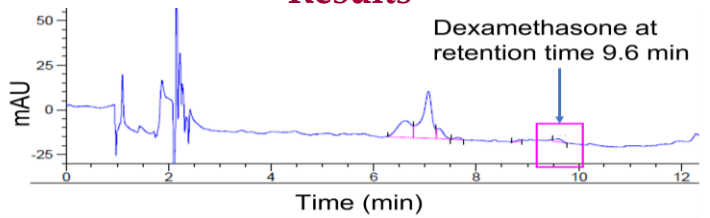

Figure 3. Detection and quantification of DEX in the brain tissue sample from a PD7 rat intraperitoneally injected with ELP loaded with DEX using HPLC.

Conclusions

1. Selective brain hypothermia (SBH) induced by the chamber was as effective as whole body hypothermia (WBH) in protecting the brain.
2. Disassembly of the ELPs in response to low pH and temperature denotes drug release and indicates the potential success of this form of targeted therapy.
3. The ELP-based delivery vehicle can then be used as a tool in future pharmacological pre-clinical studies for drug screening.

Future Directions

Inject the ELP-DEX system into the neonatal rat model of HIBD and conduct pathophysiological and behavioral analyses to determine the effectiveness of this treatment in combination with hypothermia.

References

Millar LJ et al. (2017). Frontiers in Cellular Neuroscience 11:78. MacEwan SR, Chilkoti A (2010). Peptide Science: Original Research on Biomolecules 94(1):60-77.

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