MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Optimization Of Lipid-coated Mesoporous Silica Nanoparticles For BBB Targeted Delivery Of 2-PAM To The CNS

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Background Information
The current treatment for organophosphate nerve agent (OPNA) exposure is the administration of oximes, such as pralidoxime (2-PAM), that reactivate acetylcholinesterase (AChE) to reverse the toxic buildup of acetylcholine. Unfortunately, 2-PAM does not readily cross the blood-brain barrier (BBB) to therapeutically relevant concentrations to the central nervous system (CNS). Targeted BBB drug delivery through use of nanoparticles has the potential to improve drug localization to the brain while reducing off-target side effects. This creates a need for the design of nanoparticle drug vehicles that have efficient drug loading, controlled release, stability in physiological conditions, and increased BBB penetration over current free drug formulations.
Objective
The purpose of this study is to design and optimize lipid-coated mesoporous silica nanoparticles (LC-MSNs) that translocate across the BBB to effectively deliver 2-PAM to improve AChE reactivation in the CNS after OPNA exposure.
Rationale for the research
The standard course of treatment for OPNA exposure requires large, continuous doses of oximes that still have poor BBB penetration. This emphasizes the need for alternative drug delivery methods that have the potential to improve drug accumulation in desired tissues, such as the use of nanoparticle drug vehicles.
Relationship to other areas of study
Designing nanoparticle vehicles that can efficiently deliver therapeutics across the BBB can help protect both military and civilian populations from chemical threats, as well as provide a nanoparticle platform for CNS diseases.
Methods
We have prepared MSNs and LC-MSNs with various sizes, chemistries, porosities, and lipid coatings and characterized them by TEM and DLS. The loading and release of 2-PAM in MSNs and LC-MSNs was measured by spectroscopic absorption. Targeted LC-MSNs were prepared by conjugating top-performing heavy-chain only antibodies (HcAbs) to the surface using carbodiimide chemistry. These formulations were tested in vitro using the DRAPER PREDICT96 platform and other simplified mouse BBB monolayers. Additionally, we have conducted in vivo experiments for our optimized LC-MSN formulations that have been quantified using enzyme-linked immunosorbent assay (ELISA).
Preliminary results
We determined that the composition of the lipid coating had an impact on 2-PAM loading and release in LC-MSNs with some formulations resulting in more than 40% drug loading. Additionally, we were able to conjugate BBB-penetrating HcAbs onto the LC-MSNs with different ligand densities. We evaluated the ability of BBB-targeted LC-MSNs to cross the BBB in vitro using the PREDICT96 platform showing higher transport over the non-targeted control. We also conducted in vivo studies that demonstrated an increase in LC-MSN accumulation for those conjugated with BBB-penetrating HcAbs.
Preliminary conclusions
In conclusion, we have been able to load 2-PAM into LC-MSNs and conjugated LC-MSNs with BBB-penetrating HcAbs. We were able to observe improved transport of BBB-targeted LC-MSNs over non-targeted LC-MSNs across the BBB in both in vitro and in vivo experiments.