Intranasally Administered Lectin Functionalized PEG-PLGA Nanoparticles: A Novel Drug Delivery System for the Treatment of Schizophrenia

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ABSTRACT SUMMARY
Lectin-functionalized nanoparticles prepared via self-assembly of block copolymers of polyethylene glycol (PEG) and poly(lactide-co-glycolic acid) (PLGA) have been demonstrated to enhance the delivery of the anti-psychotic drug haloperidol to the brain when delivered via the intranasal route. Striatal tissue drug concentrations 1.5-3-fold higher than that achievable with intraperitoneal injection or intravenous administration of the same nanoparticles were achieved via the intranasal route. Rat studies confirm that the delivered drug can induce the expected cataleptic effect, demonstrating the bioavailability of the drug delivered to the brain.

INTRODUCTION
Over the past two decades, there has been marked improvement in our understanding of the underlying etiology and treatment of central nervous system (CNS) disorders. However, many of the drugs used to treat these disorders lack an effective means for crossing the blood-brain barrier (BBB). Nanoparticles of sizes <150nm have shown potential for this application. Coupled with the well-documented activity of nanoparticles across various applications to control drug release following drug administration, increase the likelihood of the encapsulated drug reaching the target of interest, and reduce the dose of drug required for effective therapy, nanoparticle-based therapies for the treatment of CNS disorders are of significant interest. A number of typical and atypical antipsychotic drugs (APDs) have demonstrated effectiveness when incorporated into nanoparticles, including haloperidol, chlorpromazine, olanzapine, and risperidone. Nanoparticles loaded with APDs have been tested in rodent models using the intranasal, injectable (subcutaneous, intramuscular, intraperitoneal (IP), intravenous), and oral routes of administration to treat schizophrenia.

The self-assembly of block copolymers containing on hydrophilic block and one hydrophobic block has been demonstrated to be a particularly effective strategy for generating narrowly-dispersed nanoparticles in the size range required for effective BBB transport. However, the effective and minimally invasive delivery of nanoparticles to the brain remains a challenge to wide-spread use of such therapies. The availability of multiple routes of administration with nanoparticle drug carriers could provide patients and medical practitioners with the flexibility to choose a preferred route of administration for the patient. The intranasal route of administration provides both the fastest route to the brain and higher neural bioavailability due to greater uptake of the nanoparticle formulations relative to injection or oral administration. Further improvements in APD-loaded nanoparticle efficacy for the intranasal route may be achieved by functionalizing the particle surface for the purpose of cell-specific targeting, increasing the efficacy of nanoparticle uptake by the olfactory epithelial cells following intranasal administration. Such targeting has not yet been demonstrated using APD-loaded nanoparticle formulations.

In this work, we prepared haloperidol-loaded nanoparticles based on the self-assembly of poly(ethylene glycol)-block-poly(lactide-co-glycolic acid) (PEG-b-PLGA) block copolymers that are surface functionalized with a polymeric lectin with demonstrated binding affinity to the nasal epithelium. We hypothesize that lectin functionalization will increase the likelihood of uptake by the nasal epithelial cells and thus improve the efficacy of nanoparticle delivery to the brain for improved treatment of CNS disorders such as schizophrenia.

EXPERIMENTAL METHODS
Nanoparticles were prepared using a chloroform-water emulsion/solvent evaporation method, with PEG-b-PLGA copolymer, maleimide end-functionalized PEG-b-PLGA copolymer, and haloperidol (drug) used as the building blocks for the nanoparticles. The pendant maleimide residues were subsequently used to conjugate Solanum tuberosum lectin to the nanoparticles via a Michael addition reaction, with the efficacy of the lectin conjugation confirmed by a BCA assay. Nanoparticles were characterized by transmission electron microscopy (size/shape), nanoparticle tracking analysis (size/concentration), and zeta potential analysis (particle surface charge). In vitro drug release kinetics of haloperidol in simulated
body fluids (both endosomal and physiological pH values) were assessed over 96 hours, with drug release quantified using HPLC. The functionality of the released drug was confirmed via a probe displacement test with bovine striatal membranes ex vivo as well as in vivo catalepsy testing; while catalepsy is the side-effect of haloperidol treatment, it can be easily screened to confirm drug bioavailability upon in vivo administration. Tissues were extracted following administration and drug was extracted to assess the drug biodistribution following intravenous, interperitoneal, and intranasal administration.

RESULTS AND DISCUSSION

Lectin-functionalized haloperidol-loaded nanoparticles were successfully prepared with relatively narrow size distributions (PDI < 0.2) and sizes in the required range for transport across the blood-brain barrier (<135 nm, Fig. 1a). Drug encapsulation efficiencies of >70% were achieved with all formulations. In vitro release of haloperidol was only <8% of the loaded amount in both endolysosomal conditions as well as at physiological pH in the presence of a hydrophobic micellar domain over 96 hours, demonstrating minimal drug leakage and the potential for efficient drug transport to the targeted brain tissue. The haloperidol released from the nanoparticles was successful in displacing $[^{3}H]$ N-propylnorapomorphine and binding to bovine striatal dopamine D2 receptors, confirming the bioavailability of the released drug. (Fig. 1b)

Both lectin conjugated and non-targeted haloperidol-loaded nanoparticle formulations were found to be highly effective at inducing catalepsy, demonstrating that nanoparticles even without the targeting ligand could successfully transport drug into the brain. However, intranasal administration of STL-functionalized nanoparticles increased the brain tissue haloperidol concentrations by 1.5-3x more likely to reach their target, the D2 receptor in the striatum. This nanoparticle formulation coupled with the intranasal delivery strategy thus demonstrates potential for less invasive and improved efficacy delivery of hydrophobic drugs to the brain for the treatment of central nervous system disorders.

Figure 1. (a) TEM image of lectin-functionalized nanoparticles (b) Competitive binding of released haloperidol to bovine striatal dopamine D2 receptors

Figure 2. Olfactory bulb (top) and striatal tissue (bottom) concentrations of haloperidol following drug administration based upon the drug treatment received. All rats except those receiving empty nanoparticles were cataleptic.

CONCLUSION

Lectin-functionalized haloperidol-loaded nanoparticles given intranasally are 1.5-3x more likely to reach their target, the D2 receptor in the striatum. This nanoparticle formulation coupled with the intranasal delivery strategy thus demonstrates potential for less invasive and improved efficacy delivery of hydrophobic drugs to the brain for the treatment of central nervous system disorders.

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