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Formulation and device design to increase nose to brain drug delivery

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ABSTRACT

A major limiting factor for the treatment of central nervous system (CNS) related disorders is the inability for drug substances to cross the blood-brain barrier. Some medications may possess dose-limiting systemic side effects that hinder their ability to reach maximum effective concentrations in the CNS.

Over the last several decades, scientists have studied the ability for drugs to be transported from the nose directly to the brain, and compared to intravenous injections, many studies have reported higher brain concentrations from formulations administered intranasally. The primary focus of this paper is to review the formulation and device approaches that have been reported to increase drug delivery into the CNS through the nose-to-brain delivery pathway.

Contents

abbreviations: CNS, central nervous system; BBB, blood-brain barrier; CSF, cerebrospinal fluid; IGF-I, insulin growth factor-I; AUC, area under the curve; DTE, direct targeting efficiency; i.n., intranasal; i.v., intravenous; PEG-PLA, poly(ethylene glycol)-poly (lactic acid); PLGA, poly(lactic-*co*-glycolic acid); RSP, risperidone; RNE, risperidone nanoemulsion; RMNE, risperidone mucoadhesive nanoemulsion; SLN, solid lipid nanoparticle.

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1. Introduction

There are several barriers that a drug must overcome to treat a CNS related disorder and provide a pharmacological response. These include the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier [1]. The BBB is comprised of tight junctions, an enzymatic barrier, and transport proteins that selectively prevent substances from entering the brain interstitial fluid from the blood [2]. Over the last several decades, it has been discovered that materials can be transported directly to the brain interstitial fluid and cerebrospinal fluid when administered intranasally [3,4]. By using intranasal administration, it is possible to circumvent the barriers of the BBB by taking advantage of the only place the CNS is in direct contact with the environment, the olfactory epithelium [4]. In bypassing the BBB, drugs that normally cannot enter the CNS may be found to be therapeutically beneficial when administered intranasally. In addition, drugs that pass the BBB but require large doses to provide therapeutically relevant brain levels, may be effective at significantly lower doses, with a subsequent decrease in adverse effects [5]. In the past, invasive methods such as intraparenchymal, intrathecal, and intracerebroventricular injections have been used to achieve clinically relevant brain concentrations for therapeutic efficacy. More recently, semi-invasive methods that transiently permeabilize the BBB have been reported [6,7]. However, using targeted administration to the olfactory epithelium, it may be possible to achieve the same effects in a patient-friendly manner that is conducive for chronic therapy [1]. In animal models, it has been shown that small molecules [8], peptides [4] and even viruses [9] can reach the brain using direct nose-to-brain pathways. Direct nose-to-brain delivery refers to intranasal administration of a drug substance to the nasal cavity followed by absorption and transport of the drug directly into the brain, bypassing the BBB. Limitations of nose-to-brain delivery have also been identified, and include a relatively small volume for administration of the drug, limited surface area of the olfactory epithelium and short retention time for drug absorption [10].

Despite these potential limitations, the nasal route of administration for brain delivery has shown promise for therapeutic efficacy based on animal models and clinical trials in humans [11,12] For an in-depth review of the mechanisms and pathways by which drugs are transported to the brain from the nose, readers are pointed to previous works by Dhuria et al. [13], Pardeshi et al. [8], Lockhead et al. [14] and Baker et al. [15] The present review is focused specifically on how formulation and device design differences enhance drug uptake into the brain.

2. Nasal formulations to enhance brain drug delivery

As with other routes of drug delivery, formulation design has been shown to help in overcoming many of the barriers for direct nose-to-brain drug delivery. Table 1 provides a list of examples that have so far been reported in the literature on formulations, and their effects on nose-to-brain delivery. As can be seen in Table 1, formulations that have so far been utilized to enhance nose-to-brain delivery include: solutions, microemulsion, mucoadhesive formulations, polymeric nanoparticles, lipid-based nanoparticles as well as novel combination therapies. The formulation of choice may be greatly influenced by the physicochemical properties of the drug.

2.1. Solution based formulations

When formulating drugs as a solution (i.e., molecular dispersion), the physicochemical properties of the drug will be the driving factor enhancing absorption. Studies on direct nose-to-brain delivery with solutions have been done on a number of drugs (Table 1); including elements like manganese [47,48] and cobalt [49], to more complex small molecules like remoxipride [36] and UH-301 [44], and even proteins [11,50–52]. Thus, the physicochemical properties of the drug is an important consideration when designing direct nose-to-brain dosage forms. Passive diffusion has been shown to play a significant role in the delivery of small lipophilic molecules as reported by Kandimalla et al. from diffusion cell permeability studies with hydroxyzine [53]. To exemplify the importance of size on this drug delivery, Pardeshi et al. [8] compared the delivery of dopamine [54], a small molecule, to that of nerve growth factor, a relatively small secreted protein (MW = 26,500 Da), and observed that brain concentrations were fivefold higher for dopamine than the protein when dosed at the same concentration. Even though small lipophilic drugs are found to have the highest brain levels after intranasal administration, hydrophilic drugs often show the largest improvement in brain levels compared to other routes of administration. Raltitrexed, a hydrophilic small molecule with a logP of −0.98, was studied to assess brain levels after intranasal and intravenous administration. It was found that, depending on the section of brain, a 54–121 fold increase in the AUC was noted after intranasal administration when compared to intravenous use in rats [34]. Wang et al. performed similar experiments with methotrexate, another hydrophilic drug with logP −1.98, and found that it provided greater than 13 fold higher CSF AUC after nasal administration compared to intravenous administration [27]. When comparing the CSF concentrations from the Wang et al. study to those that use a brain tumor model [5], it can be inferred that the increase in CSF concentration may be sufficient for pharmacological activity.

Recently, brain distribution and efficacy studies have been reported with pralidoxime and obidoxime solutions [55]. Krishnan et al. [55]. report brain distribution of the compounds in rats was consistent with direct nose-to-brain delivery. Pralidoxime and obidoxime are oximes which can be used for treating organophosphate poisoning. However, their efficacy is limited by their inability to effectively cross the BBB. Krishnan et al. also measured acetylcholinesterase return from inhibition, the target for organophosphate poisoning, after intranasal administration of the medication and found that nearly 90% of enzyme activity was brought back in the olfactory region and anywhere from 4 to 13% recovered in other regions of the brain. Interestingly, it was found that a solution formulation of the oximes was preferred over the attempted chitosan based nanoemulsion or chitosan based nanoparticles due to loading efficiency and viscosity issues. This serves as an excellent example that formulations must be tailored for efficiency and compatibility with their eventual mode of delivery.

Solution formulations of macromolecules [8,56] have presented evidence of direct transport in animal studies including solutions of plasmids [57], IGF-I [51] and Nerve Growth Factor [4]. Research with arginine vasopressin [58], insulin [12], oxytocin [11] and melanocortin melanocyte-stimulating hormone/adrenocorticotropin$_{4\text{-}10}$ [59] in humans supports the delivery of macromolecules via this route.

The wide variety of substances that can be transported directly to the brain is promising for the enablement and enhancement of treatment options for CNS-related disorders. While only a limited number of the current studies in humans provide pharmacokinetic evidence for direct nose-to-brain drug delivery, many experiments have compared pharmacodynamic endpoints after intranasal and intravenous administration. Ruigrok and Lange [60] explained that pharmacodynamic-pharmacokinetic studies in animals may provide more accurate predictive models for assessing drugs undergoing direct nose-to-brain transport in humans than previously used pharmacokinetic animal models. Predictive models are needed because direct pharmacokinetic studies using brain