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STRATEGIES FOR NOSE-TO-BRAIN DRUG DELIVERY

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ABSTRACT
Intranasal drug administration is an effective method that has shown promise for delivering drugs directly to the brain. This approach is associated with many challenges, and efficacy in bypassing blood-brain barrier (BBB) is debated. This review describes the pathways of nose-to-brain drug delivery, physicochemical drug properties that influence drug uptake through the nasal epithelium, physiological barriers, methods to enhance nose-to-brain absorption, drug bioavailability and biodistribution, and intranasal devices for nose-to-brain drug delivery. The mechanism of each device is described and supporting evidence from clinical trials is presented. This paper summarizes strategies involved in nose-to-brain drug delivery and provides evidence of potential efficacy of nose-brain-delivery from clinical trials.

Keywords: Intranasal, nose-to-brain, bioavailability, biodistribution, devices, nebulizers

1. INTRODUCTION

Nose-to-brain drug delivery has emerged as a novel non-invasive route that has advantages over systemic drug administration including evasion of systemic toxicity, a better side effects profile, non-invasiveness, short time to effect onset, and increased central nervous system (CNS) bioavailability (Erdő et al. 2018; Craft et al. 2012). Intranasal insulin (INI) is the most widely used drug for nose-to-brain delivery in randomized controlled trials (RCT) due to its potential for improvement of memory, cognition, and appetite control. A review of short- and long-term clinical trials assessed INI safety in 1092 participants and showed that INI is safe and does not cause hypoglycemic episodes (Schmid et al. 2018).

The olfactory epithelium, located on the upper part of the nasal cavity, is the main absorption site for direct nose-to brain delivery (Bitter, Suter-Zimmermann, and Surber 2011). This route bypasses the blood-brain barrier (BBB) by providing direct neural connections between the olfactory epithelium and the brain (Dhuria, Hanson, and Frey 2010; Lioutas et al. 2015). Once a drug is intranasally administered, it can follow multiple pathways. The olfactory and trigeminal nerve pathways allow for most efficient nose-to-brain delivery. From the upper nasal cavity, the drug can travel through the perineural space into the subarachnoid space where the drug would be further transported into the brain tissue through the perivascular pump. In the nose, the drug may undergo mucociliary clearance allowing penetrance into the respiratory mucosa in order to be absorbed systemically. Negligible amounts of the intranasally administered drug enter the systemic circulation. The BBB acts as a deterrent for the drug present in the systemic circulation to enter the brain. An alternative route the drug may take from the respiratory mucosa is to the nasopharynx into the gastrointestinal tract (Pardeshi et al. 2013; Ruigrok and de Lange 2015). RCTs have demonstrated successful nose-to-brain insulin delivery through the use of fMRI (Kullmann et al. 2018, 2017; Brünner et al. 2016; Guthoff et al. 2010), cerebral blood flow measurements (Akintola et al. 2017; Kullmann et al. 2015; Schilling et al. 2014), cerebrospinal fluid (CSF) drug concentration levels (Born et al. 2002), and cognitive tests (Reger et al. 2008; Hallschmid et al. 2008).

The intranasal route for nose-to-brain drug delivery remains a novel, promising therapeutic alternative. This article aims to describe the pathways for nose-to-brain drug delivery, review the available information regarding bioavailability and biodistribution following intranasal administration, physicochemical properties of intranasal drugs, physiological barriers, and the evidence behind currently available non-invasive strategies that promote nose-to-brain drug delivery.

2. NOSE-TO-BRAIN DELIVERY BIOAVAILABILITY AND BIODISTRIBUTION

Quantitative pharmacokinetic evidence of direct nose-to-brain drug delivery was obtained in one clinical study, which measured concentrations of melanocortin, vasopressin, and insulin in CSF and systemic circulation after intranasal administration (Born et al. 2002). Post INI administration, CSF insulin increased within 10 minutes, peaked between 30 and 45 minutes, and remained elevated at 80 minutes (Born et al. 2002). INI did not significantly affect systemic glucose levels (Ruigrok and de Lange 2015). In terms of bioavailability and biodistribution, as human brain sampling is highly restricted, preclinical animal studies using small molecule drugs, biologics, and specialized drug delivery systems have been conducted

(Kozlovskaya, Abou-Kaoud, and Stepensky 2014; Chou and Donovan 1998; Stevens et al. 2011). In the animal studies, the area under the concentration-time curve (AUC) in the brain tissue and CSF has been used to calculate measures of extent and results have shown higher drug bioavailability when targeting the brain. This was attributed to direct nose-to-brain delivery after intranasal administration, as opposed to nose-to-systemic delivery (Ruigrok and de Lange 2015). One animal study measuring procaine, tetracaine, bupivacaine, and lidocaine concentrations in the CSF in rats after intranasal administration resulted in a relative bioavailability (AUC intranasal over AUC intra-arterial) of 43% for procaine and 100% for tetracaine, bupivacaine, and lidocaine (Chou and Donovan 1998). Intranasal administration of remoxipride showed a total bioavailability of 89% (Stevens et al. 2011). Drug targeting efficiencies (%DTE) represents the relative exposure of the brain to a drug following intranasal administrations vs systemic administration (Ruigrok and de Lange 2015). To date, the most extensive descriptive and quantitative study of brain targeting efficiency via nasal route analyzed 73 publications that reported data of 82 compounds. This study showed that the majority of drugs were characterized by a %DTE higher than 100%, which indicated a more efficient delivery to the brain after nasal administration, as compared to the systemic administration (Kozlovskaya, Abou-Kaoud, and Stepensky 2014).

These studies have confirmed the feasibility of nose-to-brain drug delivery. However, CSF and whole brain measurements do not necessarily provide accurate information of drug concentrations at the target site (Ruigrok and de Lange 2015). Qualitative and quantitative differences of factors involved in nose-to-brain transport between animals and humans may be another limitation for successful translation of preclinical evidence (de Lange 2013). Bioavailability, biodistribution, and the resulting efficacy of nose-to-brain delivery are determined by many dynamic and concurrent biological factors and processes. Therefore, advanced experimental animal studies using an integrated approach considering these components in the mathematical model should be performed to obtain more accurate and reliable results (Ruigrok and de Lange 2015).

3. PATHWAYS FOR NOSE-TO-BRAIN DRUG DELIVERY

The main target region for achieving effective nose-to-brain drug delivery is the olfactory epithelium in the upper nasal cavity. This region contains olfactory nerve cells which provide direct access to the brain and CSF (Figure 1).

3.1. Olfactory nerve transport

The olfactory epithelium is the predominant site of drug absorption for nose-to-brain delivery. Once absorbed through the olfactory epithelium, drug transport occurs along the olfactory neural cells which terminate at the olfactory bulb. From there, the drug enters the brain directly or via the CSF (Pardeshi et al. 2013). A study demonstrated successful delivery of intranasal Insulin Growth Factor-1 (IGF-1) along the olfactory nerve pathway to the brain. The study mapped the pathway along the olfactory nerve and showed activation of signaling pathways of the IGF-1 receptor in the brain (Thorne et al. 2004).

3.2. Trigeminal nerve transport

The trigeminal nerve innervates the respiratory and olfactory epithelium of nasal mucosa. After penetrating the olfactory epithelium, the drug is transported along the trigeminal nerve into the brain via the pons (Pardeshi et al. 2013). An animal study administered intranasal Interferon-Beta (IFN-β) and showed significant targeting of the drug along the trigeminal nerve pathway and brain (Thorne et al. 2008).

3.3. Perivascular pump and lymphatic transport

Drugs delivered into the olfactory epithelium are transported through the perineural space into the subarachnoid space by paracellular and lymphatic mechanisms, mainly through perivascular pumping and bulk flow. The perivascular pump mechanism depends on systolic arterial pressure. The pressure waves create a compression in the perivascular space and help move its contents forward (Crowe et al. 2018). A study showed presence of intranasally administered TR-Dex3 in the perivascular system within 20 minutes of administration (Lochhead et al. 2015).

4. PHYSICOCHEMICAL DRUG PROPERTIES

4.1. Dose & Concentration

When targeting the brain, intranasal drug administration has a significantly faster absorption rate and onset of action when compared to systemic administration. The nose-to-brain pathway achieves therapeutic effects at lower doses, reaches higher brain concentrations, and maintains the drug's efficacy while minimizing systemic side effects (Erdő et al. 2018). Most RCTs using INI have administered a dose of 40 IU and have achieved efficacy without any major adverse events (Novak et al. 2014; Akintola et al. 2017; Schilling et al. 2014; Zhang et al. 2015; Jauch-Chara et al. 2012; Xiao et al. 2017).

4.2. Molecular weight

Drugs with high molecular weight have low absorption rates due to low permeability and narrow absorption area through the endothelial basement membrane of the olfactory epithelium (Warnken et al. 2016). Drugs with molecular weights above 1000 Da show poor absorption through olfactory epithelium (Wu, Hu, and Jiang 2008). Even though insulin has a high molecular weight (5808 Da), studies have shown peptide molecules can also be absorbed through specialized pathways as previously described (Born et al. 2002; Fehm et al. 2000).

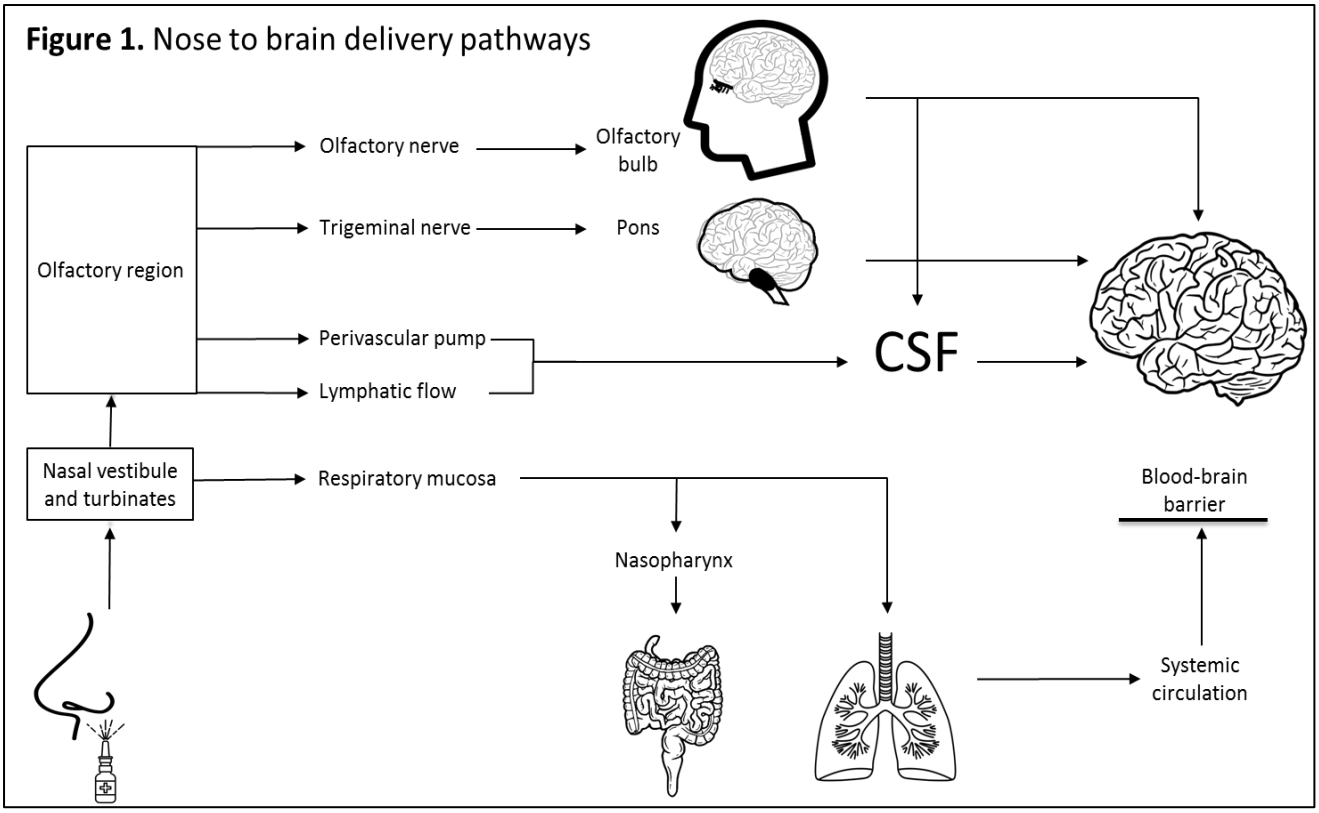

Figure 1: Once in the olfactory region, drugs can be transported into the brain bypassing the blood-brain barrier. Devices that target the nose-to-brain pathway deliver up to 47% of the administered dosage to the olfactory region. The portion that does not reach the olfactory region remains in the nasal vestibule and turbinates and undergoes local enzymatic degradation and transport via mucociliary clearance into the respiratory mucosa, nasopharynx and systemic circulation.

4.3. Lipophilicity & Hydrophilicity

Intranasal administration has led to improved brain uptake levels of lipophilic and hydrophilic drugs when compared to other routes (Warnken et al. 2016). Aqueous formulations have been shown to be more effective for intranasal drug delivery as opposed to lipophilic drugs, which are better suited for systemic administration (Warnken et al. 2016). An animal study using Raltitrexed, a hydrophilic chemotherapy drug, showed a 54-121-fold increase in AUC following intranasal administration when compared to intravenous administration (Wang, Gao, and Yun 2006).

5. PHYSIOLOGICAL BARRIERS

Nose-to-brain delivery bypasses the BBB, which contains intercellular tight junctions, endothelium-lined choroid plexus, and P-glycoprotein efflux transporters (Ruigrok and de Lange 2015). However, physiological barriers for nose-to-brain delivery include nasal epithelial tight junctions, nasal epithelial efflux transporters, mucociliary clearance, and nasal enzymatic activity (Bhise et al. 2008).

5.1. Nasal vestibule and turbinates

The nasal vestibule and lower turbinates are the first barriers that need to be overcome to reach the olfactory region and accomplish nose-to-brain delivery**.** Drugs delivered with conventional nasal delivery systems largely deposit in this regions and do not reach the upper nasal cavity where the olfactory epithelium is located (Warnken et al. 2016). Novel devices have been shown to deliver up to 45% of the administered dose past this barrier and into the olfactory epithelium (Warnken et al. 2016).

5.2. Nasal epithelium

Within the nasal cavity, the tight junctions of the nasal epithelium and its protective mucus lining act as selective filters that decrease drug permeability and their diffusion rates (Ruigrok and de Lange 2015). Mucus glycoprotein, also known as mucin, is the main component of nasal mucus. The viscoelastic properties of nasal mucus depend on mucin and water content, pH, concentrations of monovalent and divalent ions, and their physical interactions. Higher viscoelasticity leads to higher drug bioavailability due to increased nasal residence time (Erdő et al. 2018).

5.3. Mucociliary clearance

Nasal clearance transports different drugs from the olfactory epithelium to the nasopharynx through ciliary activity, increasing the risk of entering the gastrointestinal tract. This mechanism protects against inhalation of the drug (Gänger and Schindowski 2018). Risks of inhalation of INI were shown in the Exubera trial, which was terminated due to hypoglycemia and respiratory adverse events (Oleck, Kassam, and Goldman 2016). Mucociliary clearance reduces drug residence time in the nasal epithelium, which leads to decreased absorption rates (Gänger and Schindowski

2018). The mucociliary transit time in healthy subjects ranges from 2.5 to 25 minutes (Bhise et al. 2008).

5.4. Nasal metabolism

Drugs containing proteins and peptides undergo metabolism by cytochrome P450 enzymes, exopeptidases, and endopeptidases present in the nasal mucosa. This leads to local degradation of drugs, decreasing nose-to-brain delivery (Ruigrok and de Lange 2015).

5.5. P-glycoprotein efflux transport

P-glycoprotein acts as a multidrug resistance pump across the nasal mucosa and BBB. Drugs are detoxified by these efflux transporters, reducing the permeability potential of both barriers (Bhise et al. 2008).

6. STRATEGIES TO ENHANCE NOSE-TO-BRAIN DELIVERY

Nose-to-brain drug transport is highly dependent on the physicochemical characteristics of the delivered drug, the surface area of the olfactory region, and the presence of drug-specific target receptors/transporters (Illum 2000). New delivery devices, formulations, and excipients to transcend these barriers and improve CNS delivery are currently being developed and tested (Mittal et al. 2014; Crowe et al. 2018).

6.1. Auxiliary Agents

6.1.1. Enzyme inhibitors

The main purpose of these agents is to inhibit nasal metabolism. Peptides are the main target of cytochrome p450 enzymatic activity within the nasal cavity. Thus, peptidase inhibitors are the most commonly used components to improve molecule bioavailability (Hinchcliffe and Illum 1999).

6.1.2. Permeation enhancers

These excipients aim to improve the absorption of large molecular weight drugs. The mechanism of action is not completely known. Proposed mechanisms include: increasing membrane fluidity, increasing tight junction permeability, generating hydrophilic pores, diminishing viscosity, and reducing enzymatic activity (Bhise et al. 2008). Penetratin, a cell-penetrating peptide, was used in rats to successfully enhance insulin delivery into the brain (Kamei et al. 2018).

6.1.3. Mucoadhesive agents

Mucoadhesive properties alter nasal physiological mechanisms by reducing the number of open tight junctions (Hinchcliffe and Illum 1999) and enhancing the nasal residence time of the drug, resulting in an increased absorption rate (Erdő et al. 2018). Trymethyl chitosan complexes successfully enhanced insulin nose-to-brain delivery in rats (Jintapattanakit et al. 2010).

6.2. Formulations

6.2.1. Liquid formulations

Liquid formulations have been shown to have better absorption rates than lipophilic formulations (Gänger and Schindowski 2018). Insulin has been one of the most widely used drug in RCTs. Meta cresol is a colorless liquid with a sweet, tarry odor that mixes well with water (Wheeler and Taylor 2012) and is commonly used in insulin formulations such as Novolin R insulin (Novo Nordisk, Inc, Denmark), insulin lispro, insulin aspart, and insulin glulisine (Teska et al. 2014). Depending on the temperature, it can behave as a solid or liquid. Meta cresol is safe at low doses used in insulin formulations. High doses may irritate the nasopharyngeal epithelium (Wheeler and Taylor 2012).

6.2.2. Semisolid formulations

These gel-like formulations consist of both solids and liquids. Chitosan-containing formulations have been shown to improve bioadhesive properties and prolong residence time in the nasal mucosa. Semisolid gels with increased viscosity further enhance nasal residence time and drug uptake (Gänger and Schindowski 2018).

6.2.3. Particulate formulations

Nanoparticles encapsulate the drug and protect it from biological and chemical breakdown (Kulkarni et al. 2015). The P-glycoprotein efflux transporter present in the nasal epithelium and BBB can be bypassed with the use of nanocarriers (Kulkarni et al. 2015). Advantages of nanoparticle use include minimum toxicity, biocompatibility, biodegradability, physical stability, and compatibility with small molecules, peptides, and nucleic acids (Pardeshi et al. 2013).

6.2.4. Lipid-based formulations

Nanostructured lipid carriers have a wide range of uses and have less toxicity, allow for controlled or sustained release of the drug, and are able to encapsulate hydrophilic and lipophilic drugs (Selvaraj, Gowthamarajan, and Karri 2018). They achieve high efficacy by increasing absorption rates through the nasal mucosa and avoiding enzymatic breakdown (Selvaraj, Gowthamarajan, and Karri 2018).

6.3. Devices

Intranasal devices designed to enhance drug delivery to the olfactory epithelium and aid nose-to-brain delivery have been developed and tested in RCTs (Table 1). Nasal sprays that have not been specifically engineered for nose to brain drug delivery and conventional intranasal delivery devices largely deposit the administered drugs into the nasal vestibule and middle and lower turbinates (Warnken et al. 2016).

Table 1: Currently available nose-to-brain intranasal devices used in randomized controlled trials

Author	Year	N	Participants characteristics	Drug (dose)	Measurement	Conclusions
ViaNase™ (Kurve Technology, Inc. Lynwood, WA, USA) creates a vortex of nebulized particles to target the olfactory region, maximize intranasal distribution, and minimize pharyngeal deposition						
Akintola et al	2017	19 adults	20-69 years old, BMI 21-27 kg/m^2, Fasting glucose 4.5-6.0 mmol/L, Fasting insulin 2.9-8.2 pmol/L	INI Actrapid (40 IU) Placebo	MRA, Regional cortical tissue perfusion	INI improved perfusion of occipital cortical brain region and thalamus in older adults
Zhang et al	2015	28 adults	50-70 years old, HbA1c 5.4-8.0%	INI Novolin R (40 IU) Placebo	fMRI, Cognitive tests	A single dose of INI increases resting state functional connectivity in hippocampal regions in T2DM and may modify functional connectivity among brain regions regulating memory and complex cognitive behaviors
Novak et al	2014	29 adults	50-70 years old, HbA1c 5.4-8.8%	INI Novolin R (40 IU) Placebo	Regional perfusion, Vasodilation to hypercapnia, Neuropsychological evaluation	INI may improve cognitive function in T2DM patients, potentially through vasoreactivity mechanism INI appears to be safe and does not affect systemic glucose levels
AeroPump (Aero Pump, Hochheim, Germany) uses a mechanical spring mechanism with an integrated backflow block to deliver drugs and prevent contamination						
Scherer et al	2017	20 males	27-40 years old, BMI 24-26 kg/m^2	INI Actrapid (160 IU) Placebo	MRS, Gas chromatography	INI does not reduce hepatic lipid content, INI lowers BCAA levels, INI has low nose-brain uptake compared to vasopressin or melanocortin
Brunner et al	2016	16 males	Mean age 24.69 years old, Mean BMI 23.11 kg/m^2	INI Actrapid (40 IU) Placebo	fMRI, Recall mazes, Olfactometer	No enhancement of declarative memory performance
Jauch-Chara et al	2012	15 males	22-28 years old, BMI 22-23 kg/m^2	Insulin Actrapid (40 IU) Placebo	Brain ATP and PCr levels by MRS	Intranasal insulin administration considerably increases the cerebral high-energy phosphate content compared with placebo in humans

Schilling et al	2014	48 males	Mean age 23.98 years old, Right-handed	INI Actrapid (40 IU) + cortisol (30 mg) INI Actrapid (40 IU) + oral placebo Intranasal placebo + oral cortisol (30 mg) Intranasal placebo + oral placebo	CBF, Mood and hunger scales, Salivary cortisol	Insulin effects on regional CBF were present regardless of whether participants had received cortisol or not
Metered Nasal Dispenser (Pharmasystem, Markham ON, Canada) delivers 25–200 µl (median: 100 µl) per spray. It is well-suited for drugs administered daily over an extended duration						
Xiao et al	2017	9 males	45-51 years old, BMI 25-27 kg/m^2, Plasma glucose 4.8-5.0 mmol/L, Normal glucose tolerance, Plasma insulin 40-52 pmol/L	Insulin Humalog (40 IU) Placebo	Apo B100, Apo B48, Plasma lispro levels every 5 minutes for first 20 minutes after INI/placebo	INI did not affect triglyceride-rich lipoprotein secretion by liver or intestine in healthy men
Dash et al	2015	8 males	47-51 years old, BMI 23-25 kg/m^2, Fasting plasma glucose 4.8-5.0 mmol/L, Fasting plasma insulin 34-47 pmol/L	Insulin Humalog (40 IU) Placebo	Plasma glucose	INI lowers endogenous glucose production
Mistette MK Pump II, GL18 (MeadWestvaco Calmar, Hemer, Germany) uses a mechanical spring mechanism to produce a fine mist to deliver the drug into the olfactory region						
Stockhorst et al	2011	32 males	23-25 years old, BMI 22-23 kg/m^2	Insulin Insuman (120 IU) Placebo	Blood glucose, Insulin, Leptin, Epinephrine, Norepinephrine, Cortisol	Blood glucose decrease and insulin increase, while using INI, are caused by neurally-mediated signals from the brain to the pancreas
SP270+ (Nemera, La Verpillière, France) uses an actuator that produces droplets with a median size of 40 micrometers and an elliptical plume to deliver the compound into the olfactory region						
Wingrove et al	2019	16 males	20-28 years old, BMI 25-31.4 kg/m^2	Insulin Humulin (160 IU) Placebo	fMRI, Plasma glucose, Serum insulin, Serum C-peptide	fMRI showed statistically significant decreases in regional CBF within amygdala (bilateral) in response to INI compared to placebo No significant changes in plasma glucose, serum insulin, or serum C-peptide

Optimist™ (Optinose AS, Oslo, Norway) is activated by blowing into a mouthpiece in order to close the soft palate and isolate the nasal cavity while providing positive pressure						
Dale et al	2006	12 healthy adults	18-45 years old	IV midazolam (3.4 mg)	Functional disability questionnaire	Sumatriptan dose was highly effective in treating single migraine attack Optimist™ delivery device was effective, safe, and well-tolerated
				Intranasal midazolam traditional spray (6.8 mg)		
				Intranasal midazolam Optimist™ (6.8 mg)		
Djupes-land et al	2010	117 adults	18-65 years old, Moderate to severe migraine attack diagnosis	Intranasal sumatriptan (10 mg)	Pain severity score, Level of functional disability, Sustained pain-free status	Sumatriptan nasal powder administered during a migraine attack was effective and well tolerated
				Intranasal sumatriptan (20 mg)		
				Placebo		

Table 1 describes the randomized controlled trials which involved human subjects and provided evidence of nose-to-brain drug delivery such as fMRI and cerebral blood flow.

N, number of subjects; BMI, body mass index; INI, intranasal insulin; IU, international units; MRA, magnetic resonance angiography; HbA1c, hemoglobin A1c; fMRI, functional magnetic resonance imaging; T2DM, type 2 diabetes mellitus; MRS, magnetic resonance spectroscopy; BCAA, branched-chain amino acids; CBF, cerebral blood flow; ATP, adenosine triphosphate; PCr, phosphocreatine; ApoB, apolipoprotein B; IV, intravenous

6.3.1. ViaNase™ device

ViaNase™ (Kurve Technology, Inc. Lynnwood, WA, USA) electronic atomizers create a vortex of nebulized particles to maximize intranasal distribution to the upper nasal cavity and minimize pharyngeal deposition. They allow for precise electronic dosing and targeted delivery into the olfactory epithelium (Djupesland 2013). Intranasal insulin delivery using ViaNase™ devices have been shown to modify brain functional connectivity within memory networks (Zhang et al. 2015), enhance vasoreactivity and cognition (Novak et al. 2014), and improve functionality (Craft et al. 2012) without altering fasting plasma glucose and insulin measurements (Reger et al. 2008).

6.3.2. Precision Olfactory Delivery®

The Precision Olfactory Delivery® (Impel Neuropharma, Seattle, WA, USA) device features a semi disposable unit-dose format, promising consistent dose delivery and higher CNS bioavailability when compared to systemic administration. This device uses an inert liquid (hydrofluroalkane) that forms a gas propellant to deliver liquids and powders to the olfactory epithelium (Hoekman et al. 2017). This device has been shown to deliver up to 45% of the administered dose to the upper nasal cavity (Warnken et al. 2018). The device recently showed promising results in phase 1 studies in the setting of acute episodic migraine treatment using intranasal dihydroergotamine mesylate and is set to undergo phase 2 trials (Shrewsbury et al. 2019).

6.3.3. Unit Dose Systems

Unit Dose Systems (Aptar Pharma, Crystal Lake, IL, USA) are specifically designed to address the nose-to-brain pathway. This device uses a movable piston with a ball valve at the tip to deliver drugs. They feature one handed actuation and are suitable for both liquid and powder drug delivery (Djupesland 2013). This device is currently being used in an ongoing RCT, which will evaluate the safety and efficacy of three different dose levels of a third generation calcitonin gene related peptide receptor antagonist known as BHV-3500 in the acute treatment of moderate to severe migraine ("Acute Treatment Trial in Adult Subjects With Migraines - Full Text View - ClinicalTrials.Gov" NCT03872453).

6.3.4. SP270+

This device has an actuator that produces droplets with a median size of 40 micrometers and an elliptical plume. The SP270+ (Nemera, La Verpillière, France) was recently used in a double blind randomized crossover fMRI study to investigate the effect of intranasal insulin on cerebral blood flow. This study demonstrated changes in cerebral blood flow with intranasal insulin delivery when compared to placebo (Wingrove et al. 2019).

6.3.5. OptiMist™

The Optimist™ (Optinose AS, Oslo, Norway) device is activated by blowing into a mouthpiece in order to close the soft palate and isolate the nasal cavity while providing positive pressure. This delivery mechanism minimizes the risks of lung deposition during nasal administration (Djupesland et al. 2004) and optimizes delivery into the olfactory epithelium (Djupesland et al. 2006). This device has been reported to deliver up to 18% of the dosage to the upper region of the nasal cavity (Warnken et al. 2018). Recent double blind RCT using midazolam and sumatriptan nasal formulations in adults showed no serious adverse events and suggested drugs could be delivered directly into the brain through transport routes that bypass the BBB (Dale et al. 2006; Djupesland, Docekal, and Czech Migraine Investigators Group 2010).

6.3.6. Aero Pump Systems

The Aero Pump System for nasal application (Aero Pump, Hochheim, Germany) has only been used for the administration of intranasal insulin targeting the nose-to-brain delivery pathway. This device uses a mechanical spring mechanism with an integrated backflow block to deliver drugs and prevent contamination. Systematic reviews (Hallschmid et al. 2008; Benedict et al. 2007) have reviewed this device in assessing effects on memory and weight. Several double blind RCT (Schilling et al. 2014; Jauch-Chara et al. 2012; Scherer et al. 2017) have administered intranasal insulin using this device to assess the indirect effect on weight via parameters of cerebral energy metabolism (Jauch-Chara et al. 2012), Branched Chain Amino Acid levels (Scherer et al. 2017) and regional cerebral blood flow to the insular cortex (Schilling et al. 2014).

6.3.7. Mistette MK Pump II, GL18

The Mistette MK Pump II, GL18 (MeadWestvaco Calmar, Hemer, Germany) uses a mechanical spring mechanism to produce a fine mist. One RCT used this device to administer INI to the brain and assess the effect on glucose production by the pancreas. This trial reported no adverse side effects and results were indicative of brain-pancreas crosstalk (Stockhorst et al. 2011).

6.3.8 Metered Nasal Dispenser

The metered nasal dispenser (Pharmasystem, Markham ON, Canada) is a finger actuated device that can deliver 25–200 µl (median: 100 µl) per spray. It can be used in any position and is well suited for drugs administered daily over an extended duration. Drugs with a narrow therapeutic window demonstrate lower efficacy. Recent studies used the device to administer INI at a dose known to increase CSF insulin concentration and reduce hepatic glucose production (Xiao et al. 2017; Dash et al. 2015).

7. CONCLUSION

There is evidence supporting the safety and feasibility of nose-to-brain drug delivery. Nose-to-brain delivery has been confirmed by direct measurements in a clinical study and several preclinical studies. However, the current evidence for drugs targeting the brain following intranasal administration is not enough to determine the bioavailability and biodistribution parameters of the drug. Four pathways for nose-to-brain delivery have been proposed and supported by variable evidence. Currently available devices that target nose-to-brain drug delivery are moderately effective in bypassing the main physiological barriers for direct drug delivery to the brain. The advent of new nose-to-brain delivery technologies (devices and drug formulations) and the improvement of the currently available ones may increase drug delivery to the olfactory epithelium and enhance direct nose-to-brain drug delivery. These technologies will help broaden and exploit the therapeutic potential of this pathway and may shift the current paradigm of neurodegenerative diseases.

Future clinical studies are needed to determine optimal strategies based on drug formulation, device, and timing for nose-to-brain delivery. Additionally, advanced experimental, mathematical, and translational pharmacokinetic-pharmacodynamic modeling using preclinical studies with high predictive value should be performed to achieve reliable and accurate quantification of rates, extent, timing, and cerebral regions reached by drugs targeting the brain following intranasal administration.

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