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Review Article

Nose To Brain Drug Delivery System And Its Novel Approaches

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ABSTRACT

The worldwide predominance of neurological disarranges is rising and however we are still incapable to convey most sedate particles, in restorative amounts, to the brain. The blood brain obstruction, comprises of a tight layer of endothelial cells encompassed by astrocyte foot forms and these anatomical highlights constitute a noteworthy obstruction to medicate transport from the blood to the brain. One way to bypass the BBB and in this way treat infections of the brain is to utilize the nasal course of organization and store drugs at the olfactory locale of the nares; from where they travel to the brain by means of components that are still not clearly caught on; with travel over nerve strands and travel by means of a perivascular pathway both being hypothesized. The nose to brain course has been illustrated more than once in preclinical models, with both arrangement and particulate definitions. The nose to brain course has too been illustrated in human considers with arrangement and molecule definitions. The section of gadget producers into the field will empower the benefits of this conveyance course to ended up interpreted into affirmed items. The key components which decide the viability of conveyance by means of this course incorporate: conveyance to the olfactory range of the nares as restricted to the respiratory locale, a longer maintenance time at the nasal mucosal surface, entrance upgrade of the dynamic through the nasal epithelia and a lessening in sedate digestion system in the nasal depression. Signs where nose to brain items are likely to rise to begin with incorporate: neurodegeneration.

INTRODUCTION

Neurological disorders are the largest cause of disability adjusted life years (DALYS) and the second leading cause of death globally – representing 16.8% of global deaths (GBD Neurological Disorders Collaborator Group, 2017). The burden of neurological diseases is rising, with unipolar and depressive disorders predicted to become the second largest cause of morbidity by 2030 (Mathers and Loncar, 2006). In Europe, the societal cost of neurological disorders was estimated at €798 billion in 2010, a figure

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comprising direct medical as well as non-medical costs (60%) and productivity losses (40%) (Gustavsson et al., 2011). Conditions such as dementia, anxiety and addiction inflict the greatest costs on European health budgets. There is thus a pressing need for new central nervous system (CNS) medicines. The development of CNS drugs is currently hampered by the fact that these drugs have to cross the blood brain barrier (BBB) in therapeutic quantities. The BBB is a formidable barrier which prevents the passage of most compounds from the blood to the brain and comprises tight endothelial capillary cell junctions, with the capillaries surrounded by astrocyte foot processes, endothelial cells with low transcytotic capacity, efflux pumps on the endothelial cells and degradative enzymes close to the abluminal surface (Daneman and Prat, 2015). For drugs to cross the BBB, they must be less than 400 Da in molecular weight, be largely apolar and not multicyclic (Ghose et al., 2012). However a large number of compounds do not fit within these parameters, imparting serious constraint to the development of CNS actives. In actual fact 98% of drug molecules do not cross the BBB in therapeutic quantities (Pardridge, 2005) An alternative method of delivering molecules to the brain is the nose to brain route (Uchegbu et al., 2014; Godfrey et al., 2017). This route bypasses the BBB. The nose to brain route is gaining in popularity, as demonstrated by both preclinical (Godfrey et al., 2017) and human (Craft et al., 2012) studies. This route of delivery is the subject of this review and papers quoted are confined to publications which actually demonstrate delivery to the brain via established quantification techniques. We have also highlighted clinical studies, where nose to brain delivery was the intended outcome.

Nose to brain mechanism of delivery

For the purposes of drug delivery, the nasal cavity is divided into the respiratory area and the olfactory area; with the latter situated high up in the nares and the former closer to the nostrils (Sahin-Yilmaz and Naclerio, 2011). The nasal epithelium is well vascularised (Sahin-Yilmaz and Naclerio, 2011) and within the olfactory area, olfactory neurons are exposed (Purves et al., 2001) enabling the transport of drug compounds directly into the brain via the olfactory neurons. The exact mechanism by which compounds transfer from the nasal mucosa to the brain is not fully understood. However, it is known that absorption of molecules takes place at the olfactory and respiratory epithelia (Lochhead and Thorne, 2012). The routes of compound transfer through the olfactory area, of the nares, to the olfactory bulb are transcellular through either the sustentacular cells or the exposed olfactory sensory neurons (Thorne et al., 2008; Lochhead and Thorne, 2012). The route of transfer of compounds through the nasal respiratory epithelium to the brain is via the trigeminal nerves (Thorne et al., 2008; Lochhead and Thorne, 2012). Transport to other brain areas after entry to the brain (e.g. to the mid brain from the olfactory bulb or to the brain stem from the trigeminal nerve) is thought to be mainly by either extracellular convective bulk flow (Lochhead and Thorne, 2012) or via perivascular routes (Lochhead et al., 2015). The paracellular route is not thought to be significant. Intranasally dosed nanoparticles have been observed in the olfactory bulb just 5 minutes after dosing (Godfrey et al., 2017) indicating this to be the route of entry for nanoparticle delivery systems. Drug compounds, having crossed the olfactory epithelium, may also be taken up into the general circulation via the nasal vasculature; however the nasal vasculature is devoid of fenestrations and expresses the tight junction proteins (e.g. zonula occludens 1, occludin and claudin 5) (Lochhead and Thorne, 2012), thus significant transport to the general circulation via this route will be limited to low molecular weight apolar compounds. A key

advantage of the nose to brain route is the possibility of reducing plasma exposure, as has been demonstrated (Godfrey et al., 2017; Hamidovic et al., 2017), and thus eliminating peripheral side effects. The average volume of the human nasal cavity has been measured using magnetic resonance imaging as 16,449.81 mm3 ± 4288.42 mm3 with the area of the nostril opening being 357.83 mm2 ± 108.09 mm2 (Schriever et al., 2013). Nostril opening correlates positively with nasal cavity volume (Schriever et al., 2013). No difference between the average volume of the nasal cavity was observed between men and women. In human studies intranasal insulin has been located within the cerebrospinal fluid of human subjects (Born et al., 2002) and found to improve cognitive performance in Alzheimer's Disease patients (Craft et al., 2012). Studies with intranasal insulin show that there is no increase in blood insulin levels (Hamidovic et al., 2017), indicating that preferential brain delivery of peptides in humans is possible in via this route. These studies demonstrate the utility of the nose to brain route in humans, especially if peripheral drug activity should be avoided.

Limitations

There are limitations to the use of the nose to brain route and these must be acknowledged when developing new therapeutics to be administered via this route. There is a limitation on the dose volume for liquids of (100 - 250 µL) (Davis, 1999; Djupesland et al., 2014; Santos-Morales et al., 2017) and powders (20 – 50 mg depending on the bulk density of the powder) (Davis, 1999; Tepper and Johnstone, 2018; Shrewsbury et al., 2019), making the route only possible for potent drugs. Drugs that are metabolised by nasal cavity enzymes will also need to be protected from degradation and drug formulations must be non-irritant to the nasal cavity. Furthermore, from a drug development point of view, a nasal delivery device is required to deliver drugs via the nose to brain route.

Formulation	Active Pharmaceutical	Pharmacological effects	References
Solutions	Insulin	Improved memory in Alzheimer's Disease patients	(Craft et al., 2012)
	Insulin	Increased cognition in pediatric patients with 22q13 deletion syndrome	(Schmidt et al., 2009)
	Insulin	Reduced nicotine craving in smokers	(Hamidovic et al., 2017)
	Oxytocin	Reduced the post-traumatic stress disorder response in humans	(Sack et al., 2017;van Zuiden et al., 2017)
	Oxytocin	Improved ability to emotionally rate faces in patients with autistic spectrum disorder	(Quintana et al., 2017)
Solid lipid nanoparticles	Valproic acid	Protects against seizures in a rat seizure model	(Eskandari et al., 2011)
Chitosan nanoparticles	Pramipexole	Corrected motor deficits in a rat modelof Parkinson's Disease. An enhanced pharmacological response when compared to the drug in solution.	(Raj et al., 2018)

	Plasmid encodingfor red fluorescent protein	Gene expression in the striatal regionof mice brains.	(Sanchez-Ramos et al., 2018)

Formulation	Active Pharmaceutical	Pharmacological effects	References
Molecular Envelope Technology (MET) nanoparticles	Leucine-5-enkephalin	Anti-nociception in spinal, thermal and paw inflammation pain mouse and ratmodels	(Godfrey et al., 2017)
	Propofol	Sedation in a healthy rat model	(Uchegbu et al., 2014)
PLGA nanoparticles	Oxcarbazepine	Reduced seizures in a rat seizure model	(Musumeci et al., 2018)
PLGA nanoparticles coated with trimethyl chitosan	Huperzine A	Increased brain exposure when compared to uncoated PLGA nanoparticles	(Meng et al., 2018)

While clinical studies have predominantly involved the use of drugs in solution (Craft et al., 2012), in preclinical studies a variety of formulation types have been tested (Figure 1 and Table 1), such as both solutions (Thorne et al., 2008) and particulate dispersions (Godfrey et al., 2017). Most animal studies have been conducted in rodents and clinical studies have usually involved the use of a nasal drug delivery device.

Other Delivery Systems

Physical interventions aimed at increasing drug localization in particular areas is an emerging area. Focused ultrasound with the administration of microbubbles has been used to deliver gold nanoclusters to specific brain regions (Ye et al., 2018) 64Cu labelled or Texas Red labelled gold nanoclusters were delivered to the brain stem using focused ultrasound and microbubbles to localize the nanoclusters to the brain stem. The focused ultrasound causes localized microbubble cavitation at the target region and thus enables cellular uptake, with minimal delivery to the peripheral circulation (Ye et al., 2018). No histological-level tissue damage was detected in the nose, trigeminal nerve, and brain.

Clinical use of nose to brain delivery

It is clear from the foregoing account that utilizing the nose to brain route is a suitable method of achieving brain delivery of actives. As such a variety of clinical trials have been reported which utilize this route. The first report of nose to brain delivery was made in 2002 by Born et al, in which insulin along with melanocortin(4-10) and vasopressin were administered as intranasal solutions to humans and elevated levels of all three drugs detected in the cerebrospinal fluid 10 minutes after dosing (Born et al., 2002) with peak levels observed 80 minutes after dosing. This breakthrough study has paved the way for a variety of clinical studies using the nose to brain route (Chapman et al., 2013) for various disease indications

Nasal Delivery Devices

For nose to brain delivery the dose must be deposited in the olfactory region and thus a special delivery device is required (Lochhead and Thorne, 2012). These devices are either propellant activated in the case of Kurve Technologies' Vianase (Craft et al., 2017), Impel Neuropharma's Precision Olfactory Device (Shrewsbury et al., 2019) and Alchemy Pharmatech's Naltos Device (AlchemyPharmatech, 2008) or breath activated in the case of the Optinose device (Quintana et al., 2017). While nose to brain delivery is well established in the clinical trial space, it appears that devices which offer nose to brain delivery are still not associated with licensed products. Optinose's sumatriptan product – OnzetraÔ is not specifically designated as a nose to brain product but as a nasal product (AvanairPharmaceuticals, 2016). The Vianase device is an electronic atomiser which delivers liquid droplets of 15 – 20 µm in size to the entire nasal cavity, including the olfactory region (Craft et al., 2012; Craft et al., 2017; KurveTechnology, 2017). The Precision Olfactory Device delivers liquids and powders to the olfactory region of the nasal cavity using an inert liquid (hydrofluoalkane) that forms a gas propellant (ImpelNeuropharma, 2018). Alchemy Pharmatech's Naltos device (Figure 3) works by means of an inert gas which is actuated by the device to propel the powder through the nares (AlchemyPharmatech, 2008). Finally Optinose exploits the patient's own exhalation, which propels the dose deep into the nose while simultaneously isolating the oral cavity from the nasal cavity (Djupesland, 2018). Only the Optinose, Precision Olfactory Delivery and Vianase devices have been used in human nose to brain studies so far.

SUMMARY

While the BBB limits the delivery of certain drugs to the brain and, as such hampers the treatment of certain CNS disorders, accessing the brain via the nose to brain route has been demonstrated by scores of preclinical studies and about a dozen clinical trial results. Solution forms of the active have been found to be effective clinically, while both nanoparticulate formulations and solutions have been used in animal experiments. The use of nanoparticles and solution penetration enhancers improves the delivery to the brain via the nose to brain route and since there are limitations in dose volume these technologies are likely to be very important in the future. A device is needed for human studies and a number of device manufacturers have now entered the market. The route may become important for indications such as pain, AD, PTSD and intracranial tumours.

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