Evaluation of Intranasal delivery route of drug administration for brain targeting

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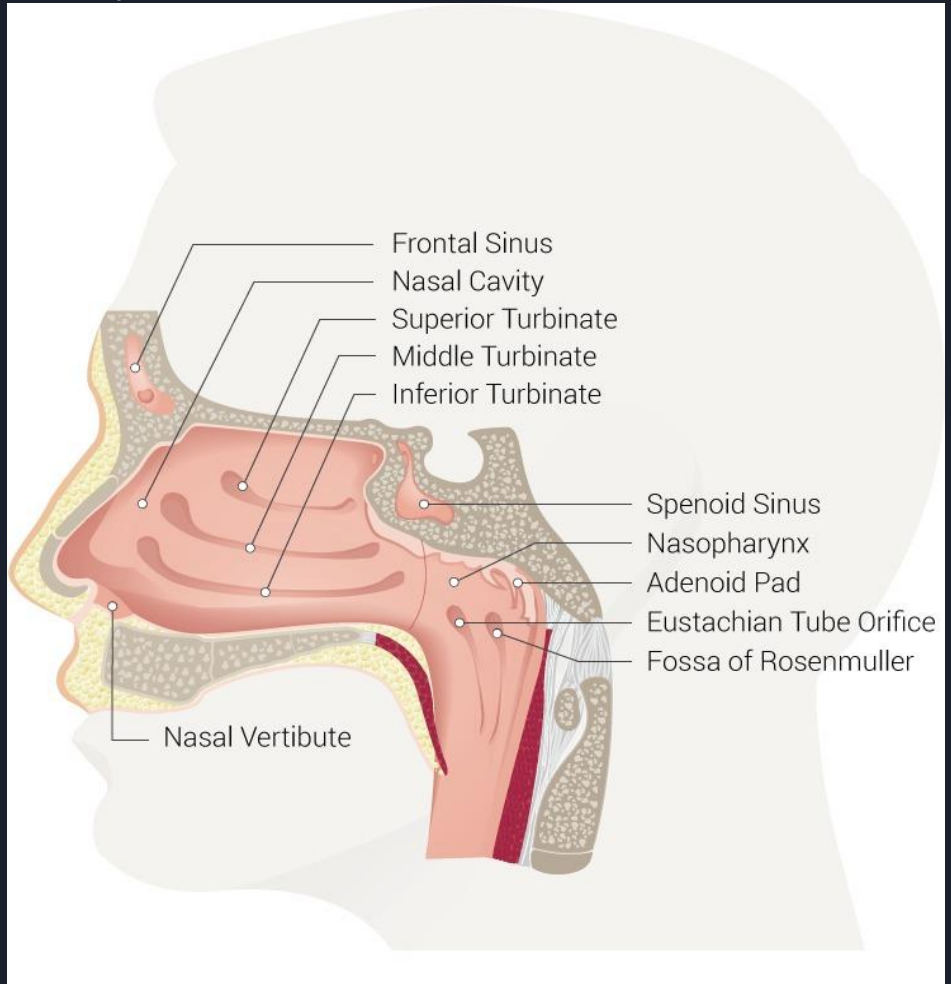
Introduction

- Nasal Pathways are a non-invasive administration route of active pharmaceutical ingredients.
- The nasal cavity provides a direct entrance to the brain and results in beneficial pharmacokinetic/pharmacodynamics (PK/PD) profile for CNS acting drugs.
- This route of administration bypasses the main physiological barriers: blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (B-CSF-B).
- At the nasal cavity the molecular diffusion bypass these barriers and the drugs are oriented directly toward the brain.

Introduction (Cont.d)

- Active pharmaceutical ingredients absorbed in the nasal mucosa can not only have local and/or systemic effect, but they can also be used to target the brain directly.
- The nasal route of drug administration has several advantages over oral or intravenous administration.
- This article gives an overview of the nose-to-brain route, focusing on the anatomy of nasal cavity and the cellular and molecular mechanisms playing an important role in the nasal drug administration and drug penetration to the brain.

Anatomy and Cellular structure of the nasal cavity



https://www.ncbi.nlm.nih.gov/books/NBK544232/#:~:text=This%20cavity%20is%20divided%20into,respiratory%20region%2C%20and%20olfactory%20region.

Models for testing direct nose-to brain delivery

- *In vivo models models*
  - For efficiently studying the nasal delivery systems, adequate in vivo models are essential
  - Selection of appropriate animal model is important for in vivo nasal absorption studies.
  - Mouse, rabbit, dog, sheep and monkey models were used as well.
  - Different animals are used for different studies.
  - Results of studies obtained from animal models do not always correlate well with those of humans.
  - The olfactory region of monkeys is similar to that of humans and lies in the upper part of the nasal cavity

Table 1
Commonly used animals in intranasal drug administration studies.

Animal	Strain	Tools for administration	Volume administered per nostril (µl)	Subject of the study	References
dogs	Labrador Retriever	mucosal atomizer device	2400	analgesic treatment	Micieli et al. (2017)
guinea pigs	Hartley	pipette/syringe	10	induction of rhinitis	Mizutani et al. (2003)
mice	CD-1	micropipette	10	insulin delivery to the brain	Salameh et al. (2015)
	Balb/c	micropipette	5	morphin administration	Westin et al. (2005)
monkeys	Rhesus monkey	modified nasal atomizer	50–200	opioid administration	Saccone et al. (2016)
rabbits	New Zealand	spray	200	insulin absorption	Najafabadi et al. (2004)
	Japanese White	nasal actuator	100	new-generation corticosteroid treatment	Sato et al. (2007)
rats	Wistar	intranasal cannula	40	minimal-stress model for intranasal administration in freely moving rats	Stevens et al. (2009)
	Sprague-Dawley	pipette/syringe	50	morphin administration	Westin et al. (2005)
sheeps	Karaman	cannula	2000	admnistration of different nasal formulations	Karasulu et al. (2008)
	Suffolk	syringe	1000	intranasal inoculation with prion to compare different scrapie strains	Moore et al. (2016)

Table 2
Characteristics of nasal cavity of different species (modified from Gizurarson, 1990).

Animal species	Mean nasal volume (ml)	Nasal length (cm)	Mean nasal epithelial surface (cm^2)	Structure of conchae	Presence of septal window	Reference
dog	20	10	210	branched conchae	no	Craven et al. (2007)
guinea pig	0.9	3.4	27	double scroll	yes	Schreider (1983)
mouse	0.03	0.5	2.8	double scroll	yes	Gross et al. (1982)
monkey	8	5.3	62	single scroll	no	Schreider (1983)
rabbit	6	5.2	61	branched conchae	no	Gizurarson (1990)
rat	0.4	2.3	14	double scroll	yes	Schreider (1983)
Sheep	114	18	327	double scroll	No	Gizurarson (1990) and Proctor and
Human	20	7.5	160	single scroll	no	Anderson (1982)

Models for testing direct nose-to brain delivery

- *In vitro models*
  - *RPMI 2650 a cell culture model of the nasal barrie*r
  - RPMI 2650 is derived from the human nasal epithelial tissue, a human nasal squamous cell carcinoma
  - It is commonly used for nasal metabolism studies and also for toxicity assays.
  - The serially passaged RPMI 2650 cells form confluent cell monolayer under controlled conditions.
  - There are two types of culture conditions of these passaged monolayers.

Models for testing direct nose-to brain delivery

- *In vitro models*
  - These passaged monolayers can be cultured under two different types of conditions: liquid-covered culture (LCC) and the air-liquid interface (ALI)
  - The preclinical assessment and comparison of solid formulations for intranasal drug delivery use RPMI 2650 cells in ALI culture as a first screening technique for cytotoxicity and permeability.

Models for testing direct nose-to brain delivery

- ***In vitro models***
  - *CaCO-2 cell line*
  - The CaCo-2 cell line, which has been utilized for three decades and can be used to assess the formulations' nasal absorption.
  - Caco-2 cell culture is the most suitable model to assess the drug absorption and permeability through the intestinal epithelia.

Models for testing direct nose-to brain delivery

- ***In vitro models***
  - *Ex vivo models*
  - Determination of toxic effects of excipients and transmucosal transport of drugs are usually performed ex vivo using nasal mucosa from experimental or slaughtered animals.
  - Frequently utilized ex vivo excised animal tissue models are obtained from rats, rabbits, dogs, sheep, monkeys, but from humans as well.
  - Studies with excised tissues are useful to obtain information on permeation, metabolism, efflux, and toxicity

Models for testing direct nose-to brain delivery

- ***In vitro models***
  - *Ex vivo models*
  - most important limitation factor is the thickness of nasal epithelial tissues of animal species and the lack of interstitial flow rate underneath the mucosa
  - Factors that affect the extent and rate of drug absorption are metabolic stability, permeation mechanisms, and formulation of the drug.
  - The well-known ex vivo nasal perfusion model for drug permeability is the Ussing chamber.
  - It is possible to quantify passive diffusion, active transport, efflux transport as well as identify and characterize (compound)-specific carrier-mediated routes of transport.

Intranasal application of different drugs for CNS indications

- *Preclinical data*
  - Several CNS drugs barely pass through the BBB and even if they can penetrate into the brain efficiently, they cause adverse effects in the periphery
  - Many intranasal medications are still in preclinical phase of development. Some of these studies are targeting memory and learning, that show potential treatment for neurodegenerative disorders like AD, PD, epilepsy and other neurotoxic events like oxidative stress and ischemia and other diseases as it can be seen

Intranasal application of different drugs for CNS indications

- Preclinical data
  - Learning and memory, neurodegenerative diseases
  - Eating regulation, obesity
  - Autoinflammatory diseases
  - Antibodies
  - Gene vectors tumors and stem cell therapies

Table 3
Short summary of some preclinical studies on intranasal drug delivery to the brain with positive outcome.

Drug name	Animal and Administration (if mentioned)	Indications	Results	References
NAP peptide	monkey, atomizer mouse	memory problems; hyperactivity; sleep deprivation	Significant difference in potency of IN *vs* i.v orexin-A. Successful memory improvement in NAP-AF64A-treated animals.	Deadwyler et al. (2007) and Gozes et al. (2000)
	mouse	Alzheimer's Disease like pathology; tauopathy, anxiety	Chronic IN NAP reduced anxiety and increased soluble tau and reduces tau hyperphosphorylation.	Alcalay et al. (2004) and Shiryaev et al. (2009)
	mouse	schizophrenia (hyperactivity and loss of visual memory)	Improved cognitive behavior model of schizophrenia	Gozes (2011)
	rat	hypoxia-induced oxidative stress	1) Attenuation in hypoxia induced ROS generation 2) restored antioxidant levels 3) modulates the expression of hypoxia responsive genes during hypobaric hypoxia.	Sharma et al. (2011)
[Ser(2)]exendin(1–9)	rat	Facilitated learning; reduced kainic-acid induced apoptosis (KAIA)	Enhaced spatial learning and attenuation of KAIA in hippocampus.	During et al. (2003)
Pituitary adenylate cyclase-activating peptide	mouse	Alzheimer's Disease (neuroprotection)	Increased sAPPα secretion. Significant reduction of soluble Aβ40 and Aβ42 peptides.	Rat et al. (2011)
Recombinant human Nerve growth factor	mouse	Alzheimer's Disease (memory, depression)	Prevent the reduction of basal forebrain ChAT + neurons. NGF-treated AD11 mice spent more time with the new object exploration. NGF-treated group had higher exploration index than PBS-treatment group.	Capsoni et al. (2002) and De Rosa et al. (2005)
L-DOPA	rat, pipette	Parkinson's Disease	IN L-DOPA group showed fewer ipsilateral, contralateral rotations and forelimb-slips compared to the vehicle group.	Chao et al. (2012)
Insulin-like Growth factor 1	mouse, drops	Spinocerebellar ataxia type 1	Improved performance on rotarod in SCA1 animals.	Vig et al. (2006)
22C4 Single-chain variable fragment antibody	rat	amyloid angiopathy, and plaque pathology, ischemic injury	Reduced mnestic deficit, improved passive avoidance and reduced glutamate overproduction.	Gorbatov et al. (2010) and Romanova et al. (2010)
Erythropoietin + Insulin-like Growth factor 1	mouse, pipette	neuroprotection in Human Immunodeficiency Virus model	Synergic effect: more effective without increasing the dose. Avoid systemic side-effects. Activation of Akt prevents tau phosphorylation.	Kang et al. (2010)
Nerve growth factor	rat, pipette	neurogenesis	Reduced seizure onset and duration. Alleviated neuronal loss.	Lei et al. (2017) and Zhu et al. (2011)
Vascular endothelial growth factor	rat	behavioral recovery, angiogenesis	Improved behavioral recovery, reduced infarct volume in middle-dose IN VEGF-treated animals.	Yang et al. (2009) and Xu et al. (2009)
Transforming growth factor β1	mouse	functional recovery, neurogenesis	Improved behavioral recovery, neurogenesis and decreased infarct volume.	Ma et al. (2008a)
Fibroblast growth factor	rat, drops	neurological functions, neurogenesis	IN bFGF improved behavioral recov. and enhanced proliferation of progenitor cells.	Ma et al. (2008b) and Wang et al. (2008)
MSC	mouse	neurotrophic factors, endogenous cerebral repair	Successfully delievered in CNS and induced recovery. Reversed SAH damage.	Van Velthoven et al. (2010) and Nijboer et al. (2018)
Galanin-like peptide	mouse, cannula attached to a 10-μl syringe	Eating regulation	Successfully delivered into the CNS.	Nonaka et al. (2008)
Leptin	rat	4-aminopyridine- and pentylenetetrazole-induced seizures	Reduced neuronal spiking and AMPA transmission.	Xu et al. (2008)
Interferon-β1b	rat, drops	Sclerosis Multiplex	IN IFN-beta showed high concentration in CNS and less systemic exposure compared to i.v.	Ross et al. (2004)
apolipoprotein B-100	mice	atherosclerosis	Attenuating atherosclerosis and inducing regulatory Tr1 cells that inhibit T effector responses to apoB-100.	Klingenberg et al. (2010)
fusion protein mCTA1–T146	mice	myasthenia gravis	Reinstating tolerance against acetylcholine receptors.	Consonni et al. (2017)
VECTOR + GENE				
Herpes simplex virus type 2 ΔRR + ICP10PK	mouse, rat	kainic acid-induced seizures (KAIS)	prevented KAIS, neuronal loss and inflammation.	Laing et al. (2006)
Filamentous bacteriophage + Myelin oligodendrocyte glycoprotein	mouse	encephalomyelitis	Improved neuronal functions, decreased proinflamatory cytokine level, induced depletion of antibodies against MOG and prevented demyelination.	Rakover et al. (2010)

Intranasal application of different drugs for CNS indications

- Clinical data

Table 4
Short summary of some clinical studies on intranasal drug delivery to the brain with positive outcome.

Drug name	Indications	References
Benzodiazepines (midazolam, diazepam)	Epilepsy	Gizurarson et al. (1999), Kälviäinen (2015), Bistritzer et al. (2000), Mahmoudian and Mohammad (2004), Mittal et al. (2006), Thakker and Shanbag (2013), Bhattacharyya et al. (2006), De Haan et al. (2010), Figgin et al. (2002), Holsti et al. (2010), Pacifici (2014), Wermeling et al. (2006), Agarwal et al. (2013), Henney et al. (2014), Ivaturi et al. (2013) and Streisand and Stanley (1995)
Insulin	memory and mood enhancement, Alzheimer's disease, Mild cognitive impairment	Benedict et al. (2004) and Kern et al. (1999) Claxton et al. (2013) and Reger et al. (2006)
	obesity (in men)	Benedict et al. (2011, 2008)
Angiotensin II	high blood pressure (with type 1 receptor block)	Derad et al. (2014)
	increases BBB permeability	Fleegal-Demotta et al. (2009) and Guillot and Audus (1991)
Melanocortin proteins	weightloss (only normal weight people)	Fehm et al. (2001) and Hallschmid et al. (2006)
Oxytocin	social anxiety disorder, autism	Kirsch (2005), Kosfeld et al. (2005), Domes et al. (2007), Heinrichs et al. (2003), Labuschagne et al. (2010) and Guastella et al. (2010)
Orexin-A	Narcolepsy	Baier et al. (2008)

Penetration enhancer techniques at nasal drug delivery route

- Formulations
  - Solutions
  - Mucoadhesive agents
  - Nanoparticles (nanosuspensions, nanoformulations)
  - Lipid based systems (microemulsions, lipid based nanoparticles)
  - Co-administration with vasoconstrictors for improved delivery
  - Permeability enhancers
- Devices to help nasal delivery
- Transporter interactions

Advantages and limitations of intranasal drug administration

Table 5
Advantages and limitations of intranasal drug administration. Modified from Lochhead and Thorne (2012).

Advantages	Limitations
Non-invasive	Limited for potent drugs
Low risks of infections	Small volumes (25–200 μL in humans)
Easy self-administration	Active mucociliary clearance
Relatively large absorption area (160 cm^2 in humans; 13.4 cm^2 in rats)	Short retention time
Large olfactory epithelium area (especially in rodents) (12.5 cm^2 in humans; 6.75 cm^2 in rats)	Enzymatic degradation by nasal cytochrome P450/peptidases/proteases (pseudo first pass effect)
Rapid absorption	Low permeability for hydrophilic drugs
Nasal submucosa is abundant in vascular and limphatic vessels	Absorption enhancers needed
No hepatic first pass metabolism of the drugs	Low nasal epithelial pH
Direct drug delivery to the brain bypassing the blood-brain barrier	Interindividual variability
	Low CNS delivery for proteins
	Nasal secretion has an influence on the absorption

Conclusion

- There are many factors to consider for intranasal or intra olfactory administration
- It is a growing area of research.
- The olfactory route, trigeminal route and vomeronasal route might be able to provide access to certain regions of the brain.
- There is still need for optimization of these routes.
- Full understanding of dosing and safety is also still needed.

Works Cited

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