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RECENT ADVANCES IN INTRANASAL DELIVERY OF THERAPEUTIC PEPTIDES

SVIATOSLAV KHARUK, ANDRII SHTURMAK, VOLODYMYR SHVADCHAK

Abstract: Treatment of neurodegenerative disorders requires delivery of drugs into the central nervous system. However, presence of the blood–brain barrier (BBB) strongly limits applicability of intravenous or oral paths for administration of drugs acting in the brain. Intranasal delivery is a promising, non-invasive strategy to bypass the BBB and deliver drugs directly to the brain. This review examines the nasal-to-brain delivery mechanisms, enhancement strategies, and therapeutic applications of drug delivery to the brain upon intranasal administration, with a focus on peptide delivery. It compares the anatomical differences in nasal cavity structure between humans and model animals used to study delivery efficacy and considers transport mechanisms, including intracellular (axonal) and extracellular (paracellular and transcellular) pathways. Peptide drugs approved for intranasal administration, such as insulin, exendin, and oxytocin as well as several peptides on the development stage are discussed in more details with insights of the influence of peptide sequence on the delivery efficiency. Finally, recent progress in various strategies to improve intranasal peptide delivery, including PEGylation, cell-penetrating peptides, and cyclodextrins are discussed.

Keywords: intranasal drug delivery, blood-brain barrier, peptide administration, olfactory transport, drug bioavailability enhancement.

1. INTRODUCTION

Neurodegenerative disorders, such as Alzheimer's, Parkinson's, and Huntington's disease affect significant fraction of elderly population and are a significant challenge for health system. Most of the currently available drugs for the treatment of diseases related to the central nervous system (CNS), are used systemically, i.e. administered orally or by injection. However, their delivery to the brain is obstructed by the blood-brain barrier (BBB) that prevents 98% of small drug molecules from entering the brain (Khawli and Prabhu, 2013). Intranasal delivery is a promising, non-invasive strategy to bypass the BBB and deliver drugs directly to the brain. Leveraging the unique anatomical connection between the nasal cavity and the CNS via the olfactory and trigeminal pathways, this route offers rapid and targeted drug transport. Intranasal delivery is particularly advantageous for neurodegenerative diseases, as it enables the administration of small molecules, peptides, and even nanoparticles with enhanced bioavailability and minimal systemic exposure (Palde et al., 2024).

Three major types of possible routes of drug delivery to the brain have been described to this day, the first being the **indirect**, systemic route, in which the drug is absorbed immediately into the systemic circulation through the nasal cavity and then through the BBB to the brain; the other, **direct** routes are the olfactory route, in which the drug passes through the olfactory epithelium into the olfactory bulb and then into the brain tissue or cerebrospinal fluid; and the third, the **trigeminal pathway**, which is named after the trigeminal nerve, in which the drug is transported directly through the trigeminal nerve.

2. The structure of the olfactory cavity and olfactory bulb in different species

The nasal cavity is anatomically connected to the brain, providing a unique and direct route for drug transport (Fig. 1). The olfactory region, located in the upper nasal cavity, contains specialized neurons whose axons extend through the cribriform plate into the olfactory bulb of the brain. Similarly, the trigeminal nerve, which innervates the nasal cavity, has branches that lead to various CNS regions. Drugs administered intranasally can travel along these neural pathways directly to the brain bypassing systemic circulation and the BBB.

The first model organism that was used to study this type of the drug delivery was the rat, rodent with strongly development sense of smell that possess relatively large nasal cavity. Later, the set of model animals used for studies of nasal delivery were extended to easier to operate mice as well as to large animals including rabbits, dogs, sheep, and monkeys. Mice and rats are good models for studying the absorption of drugs through the nose, while rabbits, dogs, and sheep are more commonly used for pharmacokinetic studies (Erdo et al., 2018).

The olfactory cavity is the first area from which the body receives information about the environment, located at the upper part of the nasal cavity, and is called the olfactory cleft. In humans, this area makes up only ~10% of the total area of the nasal cavity, while in rodents the olfactory region makes up to 50% (Fig. 1) (Keller et al., 2022).

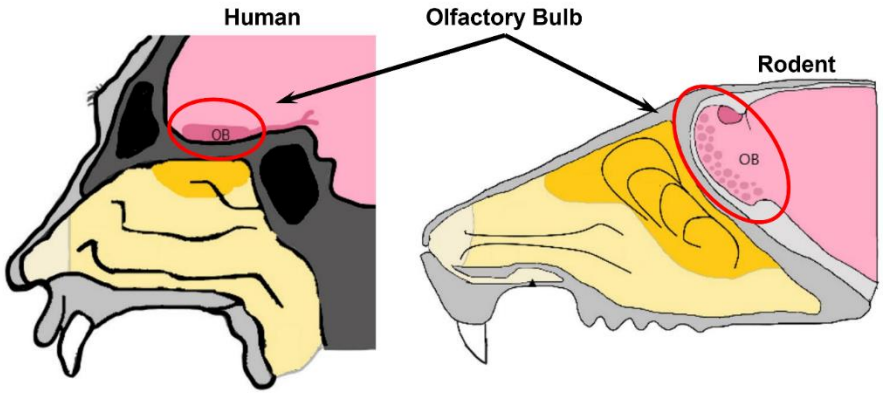

Figure 1. Olfactory bulb location and size in humans and rodents (Keller et al., 2022)

The main structure of the nose is generally similar between rodents and humans. The nasal cavity is divided into two parts that extend from the nostrils to the nasopharynx. They can be divided into three areas: vestibular, respiratory, and olfactory. In humans, the respiratory section accounts for up to 80-90%, while in rodents it covers only 50% of the nasal cavity (Harkema et al., 2006). In most respects, the morphology of the respiratory epithelium of the mouse nose is similar to that of other animals. The mouse respiratory epithelium is an example of a pseudostratified, ciliated stratified epithelium. Squamous, ciliated, and olfactory epithelia cover 7,46, and 47% of the nasal cavity, respectively. The vestibule serves as a reservoir for drips and secretions of the lateral glands and serous secretions, and the septum contains the so-called septal window, so the two nostrils cannot be considered separately (Reznik, 1990).

From the olfactory epithelium, the drug can enter the olfactory bulb of the brain. In general, the brain of mice and humans has size differences, but the basic architecture of the brain is unchanged. Many proteins in the mouse brain have much in common with human proteins. There is one very noticeable difference between the human brain and rodent brain is gyrification (the formation of brain folds), which is absent in rodents (Semple et al., 2013). Anatomical factors such as the curve from the nostrils to the nasal cavity, length and volume, structure of the shells, and the presence of a septal window can cause differences between species in the absorption of substances

from the nose (Table 1). The most important difference between humans and rodents in studies of intranasal delivery is the much large volume of nasal cavity and area of nasal epithelia comparing to the body size in rodents (Table 1). This can lead to the much faster and efficient intranasal delivery in this model organisms than in humans. The size of nasal cavity and other anatomical and physiological aspects dictate the volume of solution that can be injected into one nostril. Typical injection volumes for humans, mice and rats are 150, 3, and 13 μL, respectively (Erdo et al., 2018).

Table 1: **Comparative characteristics of the human mouse and rat nasal cavity***

	Human	Mice	Rat
Weight (kg)	70	0.03	0.25
Average volume of the nasal cavity (ml)	20	0.03	0.4
Length of the nasal cavity (cm)	7.5	0.5	2.8
Average nasal epithelial area (cm^2)	160	2.8	14
Structure of the nasal conchae	Single spiral	Double spiral	Double spiral
The presence of a Septal window	No	Yes	Yes
Elimination half-life (min) **	15	1	5
Volume injected into one nostril (μL) ***	150	3	13

* Based on the data from (Erdo et al., 2018)

** Estimated half-life calculated based on the length of the nose and the average mucus layer velocity (14 mm/min).

*** Volume of the drug administered to obtain the same volume per unit area as in humans.

3. Mechanisms of intranasal delivery to the brain

There are two main direct routes for intranasal delivery: (i) through the olfactory bulb and (ii) through the trigeminal nerve. Let's break it down. Drugs can be transported to the brain via the trigeminal nerve receptors present in the nasal cavity (Thorne et al., 2004). The trigeminal nerve enters the brain from the respiratory epithelium of the nasal passages at two areas: (1) at the Varoli's bridge; and (2) through the lamina propria near the olfactory bulbs, allowing for the penetration of drugs into both the posterior and anterior brain when administered intranasally (Schaefer et al., 2002).

The trigeminal nerve provides innervation of the respiratory and olfactory epithelium of the nasal passages. The possibility of drug transportation through the trigeminal nerve was first shown using insulin-like growth factor labeled with radioactive iodine 125I-IGF-1 (insulin-like growth factor-1). Thorne et al observed high concentrations of the radioactive label in the trigeminal nerve, trigeminal ganglion, cervical spinal cord and other CNS structures (Thorne et al., 2004).

The olfactory pathway begins with neuronal dendrites and olfactory receptors that penetrate the mucosal layer of the olfactory epithelium inside the nose to provide a sense of smell. The axons of these neurons extend centrally, passing through the subarachnoid space containing cerebrospinal fluid to transmit a synapse to mitral cells in the olfactory bulbs. From here, the neuronal endings extend to the olfactory canal, anterior olfactory nucleus, pyramidal cortex, amygdala, and hypothalamus (Kandel et al., 2014).

There have been experiments showing the role of olfactory pathways in the transportation of substances to the brain. Intranasal injection of horseradish peroxidase-conjugated agglutinin (WGA-HRP) was shown to transport along olfactory axons to olfactory bulbs in the CNS (Balin et al., 1986). Other evidence for the transport of substances by the olfactory pathway is a study showing the movement of fluorescent labels along the olfactory nerves of the lamina propria (Jansson and Bjork, 2002).

The substances via the olfactory and trigeminal pathways can be transported to the brain in different ways. These are mainly intracellular pathways, also called intracellular/intraneuronal, and extracellular/extraneuronal, which is divided into transcellular and paracellular (Fig. 2). Some authors also include the transcellular pathway in the intracellular pathway (Agrawal et al., 2018), and some authors refer to the transcellular pathway as the extracellular pathway (Keller et al., 2022).

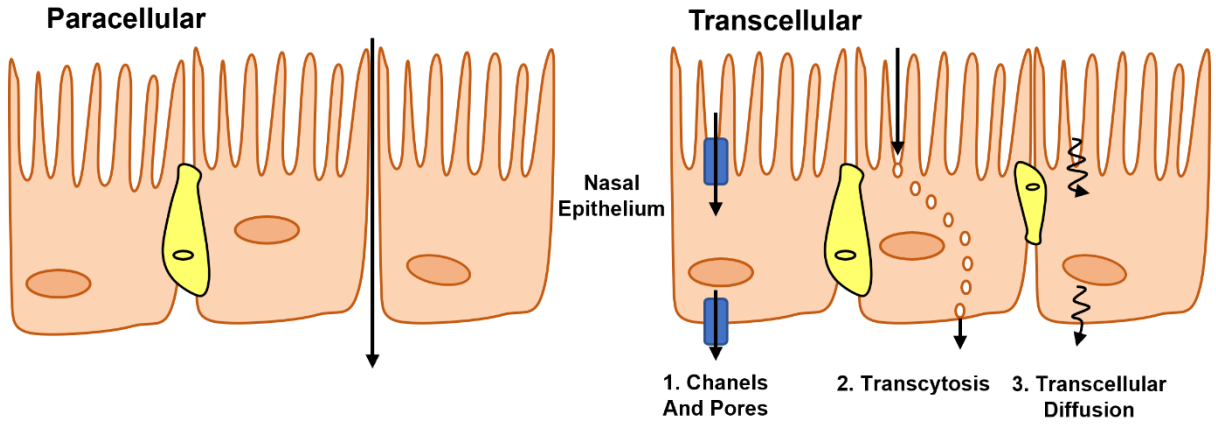

Figure 2. Transport across the nasal epithelium (Meredith et al., 2015)

The intracellular transport involves endocytosis or pinocytosis of the drug into the trigeminal or olfactory nerve. The drug moves along the axon (axonal transport), through the nerve bundle, crosses the lamina propria and reaches the olfactory bulb (via the olfactory nerve) and the brainstem (via the trigeminal nerve) (Lochhead and Thorne, 2012). Drugs can move along the nerve in endocytic vesicles, and upon entering the brain, they are exocytosed and can be distributed throughout the CNS. Passive diffusion by the intraneuronal pathway is also possible. This intraneuronal pathway is very slow, on the average, drugs are delivered via this pathway from a few hours to several days, so due to the limited speed, this intracellular mechanism is unlikely to be the predominant mode of transport for most molecules or peptides. This pathway is limited to transport of small lipophilic substances and those that have an active specific carrier (Banks, 2009).

Another pathway is the extracellular pathway, which is faster than the intracellular pathway and is used for the delivery of hydrophilic substances, peptides, and proteins. The extracellular pathway begins with either intercellular uptake by supporting cells or paracellular transport by diffusion through leaky areas of the nasal epithelium. Substances can be transported extracellularly through both the olfactory and trigeminal nerves. The drug crosses the epithelial layer via the paracellular pathway and, upon reaching the lamina propria, enters the gap between the axons and the enveloping layer. To reach the nerve cells, the drug must pass through epithelial tight junctions, which can limit its absorption (Lochhead and Thorne, 2012). However, these junctions may not be very tight, as the rate of neuronal turnover in the olfactory epithelium layer is quite high. Olfactory neurons have a short lifespan until they undergo cell death and leave the cleft (Crowe et al., 2018).

Note that passage through the lamina propria of the brain does not mean that the drug will reach the central nervous system. It can also be absorbed by blood vessels and, in turn, enter the systemic circulation. In addition, it can enter the glands or lymphatic vessels. Finally, the drug can enter the cranial nerves by extracellular diffusion, and it can also be transported to the subarachnoid space adjacent to the bridge or olfactory bulb via the trigeminal or olfactory pathways (Lochhead et al., 2015). Extracellular transport through the olfactory and trigeminal nerves is faster than intracellular transport, mainly transporting small polar, hydrophilic drugs, various proteins and peptides (Crowe et al., 2018).

Peptides can also cross the olfactory epithelium in a transcellular way. This happens by passive diffusion or receptor-mediated transcytosis. Mostly lipophilic substances are transported by the intercellular route (Spetter and Hallschmid, 2015).

4. Peptide drugs for intranasal administration

There are 4 peptide products currently known and approved by the US Food and Drug Administration (FDA) for intranasal delivery in humans: salmon calcitonin, nafarelin acetate, buserelin acetate, and desmopressin sodium acetate. All of them have a bioavailability of less than 5%. Bioavailability is the ability of a drug to be delivered to its destination and absorbed. There are also other peptides used in nasal delivery, such as exendin, galanin-like peptide (GALP), insulin, and oxytocin (Ozsoy et al., 2009).

Exendin is glucagon-like peptide (GLP-1, GLP) consisting of 39 amino acids and possessing slight negative charge (Table 2). It acts as an agonist of GLP-1 receptors, which are involved in neuroprotection and cognitive skills. The peptide was reported to enter the brain via extraneuronal route when administered intranasally and then evenly distribute in it. During et al described that intranasally administered exendin promotes neuronal survival. Receptors for exendin are located in the hippocampus and involved in memory formation and learning, through secondary transduction systems such as the adenylate cyclase and phosphatidylinositol 3-kinase pathways (During et al., 2003).

Banks et al note that the delivery of exendin via the olfactory bulb is four times more effective than intravenous administration of the peptide, although similar concentrations of exendin were delivered to other parts of the brain by both intranasal and intravenous administration (Banks et al., 2004). The effects of exendin are also associated with an improvement in the treatment of diabetes in patients. Ueno et al showed that when GLP-1 was administered before meals for two weeks, there was a restoration of early-phase insulin secretion and a decrease in glycoalbumin levels. There are also clinical trials of Exendin-4 in Alzheimer's disease, as exendin has effects related to neuronal life (Clinical Trial NCT01255163) (Ueno et al., 2014).

Galanin-like peptide (**GALP**). It is a 60-amino acid neuropeptide produced in the arcuate nucleus of the hypothalamus and the posterior pituitary gland. Galanin-like peptide, does not have any effect related to cognitive skills, while galanin is a peptide that has a similar sequence of 13 amino acids and has a positive effect on memory and cognitive skills (Beck and Pourie, 2013). A study by Nonaka et al compared the effectiveness of galanin-like peptide delivery in mice. It was found that intranasal delivery of this peptide to the brain is 20 times better than intravenous delivery and leads to a significant increase in the concentration of the peptide in the olfactory bulb within 10 minutes (Nonaka et al., 2008). Galanin-like peptide was also found to have an effect on feeding behavior in mice. Intranasal administration of the peptide for one week promotes weight loss in mice. These results suggest that intranasal administration of GALP is a viable option for people seeking to combat lifestyle-related diseases, including obesity (Shiba et al., 2010).

Insulin is the main anabolic hormone in humans, a 6kDa heterodimer consisting of A- and B-chains connected by disulfide bonds. In addition to being involved in important metabolic processes, this hormone is also involved in the central nervous system. Insulin has the ability to cross the blood-brain barrier and perform such functions as glucose utilization in the hippocampus and other parts of the brain, as well as improve signal transmission between synapses and improve memory (Luo et al., 2024). Alterations in insulin metabolism in the brain may be one of the causes of Alzheimer's disease, a neurodegenerative disease associated with memory impairment. Renner et al. and Lockhead et al. showed that insulin, after nasal administration, can be delivered to the brain extracellularly via the olfactory and trigeminal nerves (Lochhead et al., 2019), (Renner et al., 2012).

Insulin is also delivered to the brain via a specific insulin receptor. And this receptor-mediated transport initially involves the formation of the receptor-insulin complex, followed by the

internalization of insulin (Henkin, 2010). It has been shown that insulin receptor sensitivity was reduced in patients with Alzheimer's disease (Talbot et al., 2012). It has also been hypothesized that an increase in insulin concentration in the brain of patients with Alzheimer's disease may slow down the development of the disease, as activation of the insulin signaling pathway improves cognitive skills and provides neuroprotective effects. Intranasal delivery of insulin for 8 weeks (human regular insulin 4 × 40 IU/d (4 × 40 IU/day)) has been shown to improve memory and mood in the absence of any side effects (Benedict et al., 2004).

The use of intranasal insulin suggests that it may have therapeutic benefits for adults with mild cognitive impairment and Alzheimer's disease. A pilot clinical trial, in the form of a randomized, double-blind, placebo-controlled, parallel-group study in which 90 participants with Alzheimer's disease or mild cognitive impairment received daily intranasal administration of either insulin or placebo for 4 months, showed that patients taking insulin had improved short-term memory and cognitive function (Craft et al., 2012).

Oxytocyn (C*YIQNC*PLG-NH2) is a cyclic neuropeptide normally produced in the hypothalamus. It is relatively small and possesses an intramolecular disulfide bond making its molecule even more compact and easy to cross membranes. Experiments with intranasal administration of oxytocin have shown that it affects metabolic processes and eating behavior in humans proving efficiency in its delivery. It was found that intranasal delivery of oxytocin in healthy, normal-weight fasting men did not alter hunger-induced food intake for breakfast, but strongly influenced a decrease in chocolate cookie consumption when food was a reward for work. Thus, these results open up new possibilities for the use of oxytocin as a regulator of eating behavior in humans (Ott et al., 2013). Intranasal oxytocin administration has been shown to increase empathy, perception of emotions, enhance the anxiolytic effect in stressful situations, and the willingness to trust people. In a study by Zhang et al, overweight people who received a daily dose of 24 IU of oxytocin intranasally for 8 weeks lost about 9 kg of body weight and reduced their waist and hip circumference (Zhang et al., 2013). Given the lack of long-term data on the therapeutic and side effects of intranasal administration of insulin, oxytocin, and other peptides in humans, much work remains to be done to fully characterize the potential of intranasal peptide delivery in humans.

5. Other peptides studied for intranasal brain delivery

Most studies on the intranasal delivery of peptide drug candidates have been conducted in rats or mice, which are the most common experimental species for testing drug delivery to the brain, however in some cases the rabbits are also used.

Insulin-like growth factor I. Separately, the cytokines erythropoietin and insulin-like growth factor-I significantly reduce neuronal damage in rodent models of cerebral ischemia. Erythropoietin in the brain plays a neuroprotective role in many animals with brain-related injuries (Noguchi et al., 2007). Insulin-like growth factor I plays an important role in the normal development and growth of the body, it is a somatomedin and mediates some of the effects of somatotropic hormone.

The intranasal delivery of Insulin-like growth factor I was investigated in a study of neuroprotective properties of cytokines. The model object was mice injected with 125I-EPO ((3-[125I] iodothyrosyl)-erythropoietin) and 125I-IGF-I ((3-[125I] iodothyrosyl)-insulin-like growth factor-I) labelled with a radioactive tag, which were dissolved in pH 6.2 succinate buffer containing 140 mM NaCl. After injection of the drugs, the brains of mice were taken in periods from 10 to 720 minutes, homogenized, and the concentration of drugs was measured by the liquid scintillation method. According to autoradiography data, the drugs were localized to the sites of brain damage caused by middle cerebral artery occlusion (MCAO). Studies in this work and others indicate that 125I-EPO

((3-[125I] iodothyrosyl)-erythropoietin) and 125I-IGF-I ((3-[125I] iodothyrosyl)-insulin-like growth factor-I) are transported extracellularly through olfactory epithelial cells. It has also been described that IGF-1 can be transported via the triglyceride pathway, and perhaps erythropoietin can do so as well (Fletcher et al., 2009, Thorne et al., 2004).

Vasoactive intestinal peptide (VIP) is a cationic 28-amino acid peptide. The peptide performs important functions related to smooth muscle relaxation, has anti-inflammatory and immunomodulatory properties, and acts as a neurotransmitter (Delobette et al., 1997, Gololobov et al., 1998). Vasoactive intestinal peptide plays an important role in improving memory and intellectual abilities, and can be used to treat various neurological disorders such as Alzheimer's disease (Hardy and Selkoe, 2002). Studies on the intranasal delivery of vasoactive integrin peptide to the brain demonstrate that it is delivered by a direct extracellular route (Cui et al., 2013). A lipophilic analog of VIP, bearing stearyl-norleucine at position 17 demonstrated neuroprotective properties in rats with Alzheimer's disease. Radiolabeling and chromatography methods has shown that the highest amount of the peptide locates in the cerebral cortex and hypothalamus 15 minutes after injection (Gozes et al., 1996).

Orexin-A (hypocretin-1) is a neuropeptide that regulates both sleep and appetite. This hormone is secreted in the hypothalamus and orexin-A receptors are located on neurons in various parts of the brain, which allows it to activate areas associated with sleep and lack of sleep after release (Hagan et al., 1999). Hypocretin is delivered to the brain for its therapeutic potential in the treatment of narcolepsy and obesity (Fujiki et al., 2003). The delivery of hypocretin-1 to the rat brain was studied using hypocretin with 125I radiolabel. The highest concentration of the drug was found in the olfactory bulbs, 30 minutes after intranasal administration (2.2 nM). This suggests that the drug is delivered by extracellular mechanisms via the olfactory pathway and the delivery efficacy is relatively low. (Dhuria et al., 2009).

Exendin (9-39) is a selective GLP-1 receptor antagonist. It inhibits the formation of intracellular cAMP induced by GLP-1. Intranasal administration of exendin (9-39) has been shown to have a positive effect on cognitive function and neuronal survival. The study was conducted on mice intranasally injected with radiolabeled exendin (9-39). The brains were taken at 2-10 minutes after dissection and preparation of the supernatant, and the amount of the drug was measured by high-performance liquid chromatography (HPLC). The results of the study indicate that the drug very quickly enters the olfactory bulb of the brain and after intranasal administration was found in the hippocampus, cerebellum, brain stem and cerebrospinal fluid. The raped delivery points at extra-neuronal route of the exendin (9-39) transport from the nose to the brain (Banks et al., 2004).

Vasopressin is a hormone that has been identified as a modulator of emotional social behavior and is associated with neuropsychiatric disorders characterized by social dysfunction. Intranasally administered vasopressin has great therapeutic potential for the treatment of mental disorders characterized by deficits in social perception, motivation and affective behavior, such as autism, anxiety, depression and schizophrenia (Meyer-Lindenberg et al., 2011). It has been shown that vasopressin is transported to the brain from the nasal cavity by an indirect route, namely, extraneuronal. The concentration of vasopressin has been determined in mice brain using functional magnetic resonance imaging (Galbusera et al., 2017), and the amount of delivered vasopressin in cerebrospinal fluid and blood has been determined in humans by radioimmunoassay (RIA) (Born et al., 2002).

R8-Aβ(25-35) peptide is a synthetic peptide that combines a polyarginine sequence that helps the peptide penetrate membranes and a part of the amyloid beta segment. The delivery of this peptide to the brain upon intranasal administration was studied using a fluorescein conjugated to the peptide in the mouse model and 0.5-24 hours delivery times. The results suggest that it is

transported via the direct extracellular route. R8-Aβ(25-35) was developed as an inhibitor of Aβ fibril formation and octaarginine moiety was added to increase the solubility and cell permeability, There are reports showing that daily administration of the peptide reduces the formation of amyloid-beta in the brain of APP/PS1 transgenic mice (Cheng et al., 2017).

Table 2. Intranasal delivered peptides and their characteristics

Name	Length	MW, Da	Net charge	% of hydrophobic*	Reference
Approved as drugs					
Exendin	39	4190	-3	41	During et al., 2003
Galanin-like peptide	60	6472	+1	47	Beck and Pourie, 2013
Insulin	51	5795	-1	39	Luo et al., 2024
Not yet approved					
Insulin-like growth factor I	195	7650	+22	39	Noguchi et al., 2007
Vasoactive intestinal peptide	28	2800	+3	43	Gololobov et al., 1998
Orexin-A	32	3500	-1	41	Hagan et al., 1999
Exendin (9-39)	31	3400	-1	42	Banks et al., 2004
Vasopressin	9	1080	+1	22	Meyer-Lindenberg et al., 2011
R8-Aβ (25-35)	18	2250	+8	28	Cheng et al., 2017

6. Improvements of intranasal delivery of peptides

PEGylation involves chemical modification with polyethylene glycol and is considered to be an effective method to improve the penetrating ability of peptides in vivo (Moreira Brito et al., 2022). It has been well documented that this technique extends the biological lifespan of peptides by reducing their proteolysis (Harris and Chess, 2003). PEGylation also provides flexibility, as it allows easy modification of pharmacological profiles by decreasing or increasing the molecular weight of polyethylene glycol. In particular, increasing the molecular weight of polyethylene glycol increases the stability of the peptide, but may lead to interference with the biological functions of the drug. Therefore, it is important to choose the right size of PEG unit to achieve a balance between biological activity and drug stability. In addition, PEGylation reduces the patient's immune response to the administered peptides (Veronese and Pasut, 2005). Increased stability and biological lifespan of the therapeutic GLP-1 peptide calcitonin, when delivered intranasally using polyethylene glycol (mono-PEG), has been proven (Lee et al., 2003).

PEGylation of peptides for improvement of their delivery by intranasal administration was tested in diabetic mice (Kim et al., 2012). Non-invasive delivery systems are much more convenient for diabetes patients as they alleviate the pain and discomfort associated with injections. However, the bioavailability of intranasally administered therapeutic peptides is often low (in most cases <10%), which is explained by the degradation of peptides by proteolysis in the nasal mucosa.

The first clinically available incretin-like drug, exendin-4 is a peptidase-resistant glucagon-like substance. As a GLP-1 receptor antagonist, exendin-4 has many glucoregulatory effects, such as enhancing glucose-dependent insulin secretion, suppressing glucagon secretion, reducing gastric motility, and improving pancreatic endocrine function. However, its therapeutic use is limited by the need for frequent injections. In addition, intranasally administered exendin-4 has a bioavailability of only 1.7% (Gedulin et al., 2008). Thus, it makes sense to develop a low-molecular-weight polyethylene glycol conjugated with exendin-4 available for intranasal administration.

Cell-penetrating peptides (CPP) attract great interest due to their ability to improve cellular uptake of poorly internalized conjugated bioactive macromolecules (Snyder and Dowdy, 2004). Most commonly used cell-penetrating peptides include human immunodeficiency TAT peptides (Vives et al., 1997), oligoarginine (Mitchell et al., 2000) and amphipathic peptides, such as *Drosophila* homeodomain, or penetratin (Derossi et al., 1994).

The strategy of using cell-penetrating peptides is promising for the delivery of therapeutic peptides and proteins through the intestine or nose, as they provide higher bioavailability and show no visible negative effects on biological membranes (Morishita et al., 2007). Scientists have shown that the non-invasive delivery of therapeutic peptides and proteins has been significantly improved by co-administration of penetratin (RQIKIWFQNRRMKWKK) with these drugs (Khafagy el et al., 2009). In attempt to improve properties of penetratin as a vector, its analogue, Shuffle (R,K fix) 2 (RWFKIQMQIRRWKNKK) was developed (Khafagy et al., 2010). This significantly improved the bioavailability of insulin via the intranasal route compared to penetratin alone, with no detectable damage to brain membranes. The mechanism by which penetratin and Shuffle (R,K fix) 2 enhance nasal drug absorption across the cell membrane is not clear but it is expected to be associated with intermolecular binding of drugs to cell-penetrating peptides as a certain ratio between penetratin and insulin is required to maximize nasal insulin delivery (Khafagy et al., 2010) .

Cyclodextrins are cyclic oligoglucosides containing 5-10 glucose residues. They are used to improve the nasal absorption of small molecules and peptide drugs by increasing their water solubility or enhancing their absorption into the nasal mucosa. The use of cyclodextrins in dosage forms has not shown any side effects (Merkus et al., 1999).

Cyclodextrins are used as enhancers of the absorption of calcitonin, glucagon, insulin, and granulocyte colony growth factor. Calcitonin has been delivered intranasally in rats and rabbits together with methylated β-cyclodextrin as an absorption enhancer (Schipper et al., 1995). Studies indicate that usage of methyl, dimethyl and trimethyl β-cyclodextrins can improve intranasal delivery of calcitonin to the rabbit brain (Schipper et al., 1995).

When liquid and powdered variations of glucagon were administered intranasally together with dimethyl β-cyclodextrin, it resulted in approximately 80% bioavailability of the drug in the rabbit brain. A decrease in the amount of dimethyl β-cyclodextrin administered with glucagon shows a decrease in the absorption of the peptide by the nasal epithelium (Pontiroli et al., 1989).

For insulin, the absolute bioavailability after intranasal administration into the rats' nose almost doubled with the addition of dimethyl β-cyclodextrin (increase from 3 to 5%) (Merkus et al., 1991). Studies indicate that usage of dimethyl β-cyclodextrin is much more effective than other types of cyclodextrins (Merkus et al., 1991). When powdered insulin was used in combination with dimethyl beta-cyclodextrin, the intranasal delivery of the peptide increased to 13%. When modified cyclodextrins were used, the maximum delivery of 16% could be achieved (Watanabe et al., 1992). However, when unmodified cyclodextrin was added to dissolved insulin, the increase in bioavailability was insignificant as was shown in rabbit model (Schipper et al., 1993).

7. Conclusions

The delivery of therapeutic peptides to the brain remains a significant challenge due to the protective nature of the blood-brain barrier (BBB), which prevents the majority of drugs from crossing into the central nervous system (CNS). Intranasal drug delivery has emerged as a promising non-invasive strategy to bypass the BBB by leveraging direct routes such as the olfactory and trigeminal pathways. It allows not only improve the delivery but also decrease the side effects on other organs. There are several peptides for which intranasal delivery to the brain is currently well developed, including insulin, exendin, and vasoactive intestinal peptides. The maximal size of peptides that can be delivered depends on the possible route. Non-specific delivery is efficient for small, up to 30 amino acid, cationic lipophilic peptides, while receptor-mediated delivery is known

even for some large peptides. The bioavailability upon intranasal delivery remains relatively low even in the best cases rarely exceeding 10%. The intranasal delivery of peptides to the brain can be enhanced by modifying its sequence, PEGylation, co-administration with enhancers like cyclodextrins or cell-penetrating peptides. The studies of the intranasal delivery are performed predominantly in rodent models using radiolabeling or fluorescence methods. Advances in the field of intranasal delivery of therapeutic peptides hold potential for addressing the growing prevalence of CNS disorders such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis.

References

AGRAWAL, M., SARAF, S., SARAF, S., ANTIMISIARIS, S. G., CHOUGULE, M. B., SHOYELE, S. A. & ALEXANDER, A. 2018. Nose-to-brain drug delivery: An update on clinical challenges and progress towards approval of anti-Alzheimer drugs. J Control Release, 281, 139-177.

BALIN, B. J., BROADWELL, R. D., SALCMAN, M. & EL-KALLINY, M. 1986. Avenues for entry of peripherally administered protein to the central nervous system in mouse, rat, and squirrel monkey. J Comp Neurol, 251, 260-80.

BANKS, W. A. 2009. Characteristics of compounds that cross the blood-brain barrier. BMC Neurol, 9 Suppl 1, S3.

BANKS, W. A., DURING, M. J. & NIEHOFF, M. L. 2004. Brain uptake of the glucagon-like peptide-1 antagonist exendin(9-39) after intranasal administration. J Pharmacol Exp Ther, 309, 469-75.

BECK, B. & POURIE, G. 2013. Ghrelin, neuropeptide Y, and other feeding-regulatory peptides active in the hippocampus: role in learning and memory. Nutr Rev, 71, 541-61.

BENEDICT, C., HALLSCHMID, M., HATKE, A., SCHULTES, B., FEHM, H. L., BORN, J. & KERN, W. 2004. Intranasal insulin improves memory in humans. Psychoneuroendocrinology, 29, 1326-34.

BORN, J., LANGE, T., KERN, W., MCGREGOR, G. P., BICKEL, U. & FEHM, H. L. 2002. Sniffing neuropeptides: a transnasal approach to the human brain. Nat Neurosci, 5, 514-6.

CHENG, Y. S., CHEN, Z. T., LIAO, T. Y., LIN, C., SHEN, H. C., WANG, Y. H., CHANG, C. W., LIU, R. S., CHEN, R. P. & TU, P. H. 2017. An intranasally delivered peptide drug ameliorates cognitive decline in Alzheimer transgenic mice. EMBO Mol Med, 9, 703-715.

CRAFT, S., BAKER, L. D., MONTINE, T. J., MINOSHIMA, S., WATSON, G. S., CLAXTON, A., ARBUCKLE, M., CALLAGHAN, M., TSAI, E., PLYMATE, S. R., GREEN, P. S., LEVERENZ, J., CROSS, D. & GERTON, B. 2012. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol, 69, 29-38.

CROWE, T. P., GREENLEE, M. H. W., KANTHASAMY, A. G. & HSU, W. H. 2018. Mechanism of intranasal drug delivery directly to the brain. Life Sci, 195, 44-52.

CUI, X., CAO, D. Y., WANG, Z. M. & ZHENG, A. P. 2013. Pharmacodynamics and toxicity of vasoactive intestinal peptide for intranasal administration. Pharmazie, 68, 69-74.

DELOBETTE, S., PRIVAT, A. & MAURICE, T. 1997. In vitro aggregation facilities beta-amyloid peptide-(25-35)-induced amnesia in the rat. Eur J Pharmacol, 319, 1-4.

DEROSSI, D., JOLIOT, A. H., CHASSAING, G. & PROCHIANTZ, A. 1994. The third helix of the Antennapedia homeodomain translocates through biological membranes. J Biol Chem, 269, 10444-50.

DHURIA, S. V., HANSON, L. R. & FREY, W. H., 2ND 2009. Intranasal drug targeting of hypocretin-1 (orexin-A) to the central nervous system. J Pharm Sci, 98, 2501-15.

DURING, M. J., CAO, L., ZUZGA, D. S., FRANCIS, J. S., FITZSIMONS, H. L., JIAO, X., BLAND, R. J., KLUGMANN, M., BANKS, W. A., DRUCKER, D. J. & HAILE, C. N. 2003. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat Med, 9, 1173-9.

ERDO, F., BORS, L. A., FARKAS, D., BAJZA, A. & GIZURARSON, S. 2018. Evaluation of intranasal delivery route of drug administration for brain targeting. Brain Res Bull, 143, 155-170.

FLETCHER, L., KOHLI, S., SPRAGUE, S. M., SCRANTON, R. A., LIPTON, S. A., PARRA, A., JIMENEZ, D. F. & DIGICAYLIOGLU, M. 2009. Intranasal delivery of erythropoietin plus insulin-like growth factor-I for acute neuroprotection in stroke. Laboratory investigation. J Neurosurg, 111, 164-70.

FUJIKI, N., YOSHIDA, Y., RIPLEY, B., MIGNOT, E. & NISHINO, S. 2003. Effects of IV and ICV hypocretin-1 (orexin A) in hypocretin receptor-2 gene mutated narcoleptic dogs and IV hypocretin-1 replacement therapy in a hypocretin-ligand-deficient narcoleptic dog. Sleep, 26, 953-9.

GALBUSERA, A., DE FELICE, A., GIRARDI, S., BASSETTO, G., MASCHIETTO, M., NISHIMORI, K., CHINI, B., PAPALEO, F., VASSANELLI, S. & GOZZI, A. 2017. Intranasal Oxytocin and Vasopressin Modulate Divergent Brainwide Functional Substrates. Neuropsychopharmacology, 42, 1420-1434.

GEDULIN, B. R., SMITH, P. A., JODKA, C. M., CHEN, K., BHAVSAR, S., NIELSEN, L. L., PARKES, D. G. & YOUNG, A. A. 2008. Pharmacokinetics and pharmacodynamics of exenatide following alternate routes of administration. Int J Pharm, 356, 231-8.

GOLOLOBOV, G., NODA, Y., SHERMAN, S., RUBINSTEIN, I., BARANOWSKA-KORTYLEWICZ, J. & PAUL, S. 1998. Stabilization of vasoactive intestinal peptide by lipids. J Pharmacol Exp Ther, 285, 753-8.

GOZES, I., BARDEA, A., RESHEF, A., ZAMOSTIANO, R., ZHUKOVSKY, S., RUBINRAUT, S., FRIDKIN, M. & BRENNEMAN, D. E. 1996. Neuroprotective strategy for Alzheimer disease: intranasal administration of a fatty neuropeptide. Proc Natl Acad Sci U S A, 93, 427-32.

HAGAN, J. J., LESLIE, R. A., PATEL, S., EVANS, M. L., WATTAM, T. A., HOLMES, S., BENHAM, C. D., TAYLOR, S. G., ROUTLEDGE, C., HEMMATI, P., MUNTON, R. P., ASHMEADE, T. E., SHAH, A. S., HATCHER, J. P., HATCHER, P. D., JONES, D. N., SMITH, M. I., PIPER, D. C., HUNTER, A. J., PORTER, R. A. & UPTON, N. 1999. Orexin A activates locus coeruleus cell firing and increases arousal in the rat. Proc Natl Acad Sci U S A, 96, 10911-6.

HARDY, J. & SELKOE, D. J. 2002. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science, 297, 353-6.

HARKEMA, J. R., CAREY, S. A. & WAGNER, J. G. 2006. The nose revisited: a brief review of the comparative structure, function, and toxicologic pathology of the nasal epithelium. Toxicol Pathol, 34, 252-69.

HARRIS, J. M. & CHESS, R. B. 2003. Effect of pegylation on pharmaceuticals. Nat Rev Drug Discov, 2, 214-21.

HENKIN, R. I. 2010. Intranasal insulin: from nose to brain. Nutrition, 26, 624-33.

JANSSON, B. & BJORK, E. 2002. Visualization of in vivo olfactory uptake and transfer using fluorescein dextran. J Drug Target, 10, 379-86.

KANDEL, E. R., J.H., S., T.M., J., S.A., S., A.J., H. & S., M. 2014. Smell and Taste: The Chemical Senses. Principles of Neural Science, Fifth Edition. New York, NY: McGraw-Hill Education.

KELLER, L. A., MERKEL, O. & POPP, A. 2022. Intranasal drug delivery: opportunities and toxicologic challenges during drug development. Drug Deliv Transl Res, 12, 735-757.

KHAFAGY EL, S., MORISHITA, M., ISOWA, K., IMAI, J. & TAKAYAMA, K. 2009. Effect of cell-penetrating peptides on the nasal absorption of insulin. J Control Release, 133, 103-8.

KHAFAGY , S., MORISHITA, M. & TAKAYAMA, K. 2010. The role of intermolecular interactions with penetratin and its analogue on the enhancement of absorption of nasal therapeutic peptides. Int J Pharm, 388, 209-12.

KHAWLI, L. A. & PRABHU, S. 2013. Drug delivery across the blood-brain barrier. Mol Pharm, 10, 1471-2.

KIM, T. H., PARK, C. W., KIM, H. Y., CHI, M. H., LEE, S. K., SONG, Y. M., JIANG, H. H., LIM, S. M., YOUN, Y. S. & LEE, K. C. 2012. Low molecular weight (1 kDa) polyethylene glycol conjugation markedly enhances the hypoglycemic effects of intranasally administered exendin-4 in type 2 diabetic db/db mice. Biol Pharm Bull, 35, 1076-83.

LEE, K. C., PARK, M. O., NA, D. H., YOUN, Y. S., LEE, S. D., YOO, S. D., LEE, H. S. & DELUCA, P. P. 2003. Intranasal delivery of PEGylated salmon calcitonins: hypocalcemic effects in rats. Calcif Tissue Int, 73, 545-9.

LOCHHEAD, J. J., KELLOHEN, K. L., RONALDSON, P. T. & DAVIS, T. P. 2019. Distribution of insulin in trigeminal nerve and brain after intranasal administration. Sci Rep, 9, 2621.

LOCHHEAD, J. J. & THORNE, R. G. 2012. Intranasal delivery of biologics to the central nervous system. Adv Drug Deliv Rev, 64, 614-28.

LOCHHEAD, J. J., WOLAK, D. J., PIZZO, M. E. & THORNE, R. G. 2015. Rapid transport within cerebral perivascular spaces underlies widespread tracer distribution in the brain after intranasal administration. J Cereb Blood Flow Metab, 35, 371-81.

LUO, D., NI, X., YANG, H., FENG, L., CHEN, Z. & BAI, L. 2024. A comprehensive review of advanced nasal delivery: Specially insulin and calcitonin. Eur J Pharm Sci, 192, 106630.

MEREDITH, M. E., SALAMEH, T. S. & BANKS, W. A. 2015. Intranasal Delivery of Proteins and Peptides in the Treatment of Neurodegenerative Diseases. AAPS J, 17, 780-7.

MERKUS, F. W., VERHOEF, J. C., MARTTIN, E., ROMEIJN, S. G., VAN DER KUY, P. H., HERMENS, W. A. & SCHIPPER, N. G. 1999. Cyclodextrins in nasal drug delivery. Adv Drug Deliv Rev, 36, 41-57.

MERKUS, F. W., VERHOEF, J. C., ROMEIJN, S. G. & SCHIPPER, N. G. 1991. Absorption enhancing effect of cyclodextrins on intranasally administered insulin in rats. Pharm Res, 8, 588-92.

MEYER-LINDENBERG, A., DOMES, G., KIRSCH, P. & HEINRICHS, M. 2011. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat Rev Neurosci, 12, 524-38.

MITCHELL, D. J., KIM, D. T., STEINMAN, L., FATHMAN, C. G. & ROTHBARD, J. B. 2000. Polyarginine enters cells more efficiently than other polycationic homopolymers. J Pept Res, 56, 318-25.

MOREIRA BRITO, J. C., CARVALHO, L. R., NEVES DE SOUZA, A., CARNEIRO, G., MAGALHAES, P. P., FARIAS, L. M., GUIMARAES, N. R., VERLY, R. M., RESENDE, J. M. & ELENA DE LIMA, M. 2022. PEGylation of the antimicrobial peptide LyeTx I-b maintains structure-related biological properties and improves selectivity. Front Mol Biosci, 9, 1001508.

MORISHITA, M., KAMEI, N., EHARA, J., ISOWA, K. & TAKAYAMA, K. 2007. A novel approach using functional peptides for efficient intestinal absorption of insulin. J Control Release, 118, 177-84.

NOGUCHI, C. T., ASAVARITIKRAI, P., TENG, R. & JIA, Y. 2007. Role of erythropoietin in the brain. Crit Rev Oncol Hematol, 64, 159-71.

NONAKA, N., FARR, S. A., KAGEYAMA, H., SHIODA, S. & BANKS, W. A. 2008. Delivery of galanin-like peptide to the brain: targeting with intranasal delivery and cyclodextrins. J Pharmacol Exp Ther, 325, 513-9.

OTT, V., FINLAYSON, G., LEHNERT, H., HEITMANN, B., HEINRICHS, M., BORN, J. & HALLSCHMID, M. 2013. Oxytocin reduces reward-driven food intake in humans. Diabetes, 62, 3418-25.

OZSOY, Y., GUNGOR, S. & CEVHER, E. 2009. Nasal delivery of high molecular weight drugs. Molecules, 14, 3754-79.

PALDE, C., BAROT, T., CHAKRABORTHY, G. S. & PATEL, L. D. 2024. PEPTIDE DELIVERY VIA NASAL ROUTE: EXPLORING RECENT DEVELOPMENTS AND APPROACHES. International Journal of Applied Pharmaceutics, 16, 46-56.

PONTIROLI, A. E., ALBERETTO, M., CALDERARA, A., PAJETTA, E. & POZZA, G. 1989. Nasal administration of glucagon and human calcitonin to healthy subjects: a comparison of powders and spray solutions and of different enhancing agents. Eur J Clin Pharmacol, 37, 427-30.

RENNER, D. B., SVITAK, A. L., GALLUS, N. J., ERICSON, M. E., FREY, W. H., 2ND & HANSON, L. R. 2012. Intranasal delivery of insulin via the olfactory nerve pathway. J Pharm Pharmacol, 64, 1709-14.

REZNIK, G. K. 1990. Comparative anatomy, physiology, and function of the upper respiratory tract. Environ Health Perspect, 85, 171-6.

SCHAEFER, M. L., BOTTGER, B., SILVER, W. L. & FINGER, T. E. 2002. Trigeminal collaterals in the nasal epithelium and olfactory bulb: a potential route for direct modulation of olfactory information by trigeminal stimuli. J Comp Neurol, 444, 221-6.

SCHIPPER, N. G., ROMEIJN, S. G., VERHOEF, J. C. & MERKUS, F. W. 1993. Nasal insulin delivery with dimethyl-beta-cyclodextrin as an absorption enhancer in rabbits: powder more effective than liquid formulations. Pharm Res, 10, 682-6.

SCHIPPER, N. G., VERHOEF, J. C., ROMEIJN, S. G. & MERKUS, F. W. 1995. Methylated beta-cyclodextrins are able to improve the nasal absorption of salmon calcitonin. Calcif Tissue Int, 56, 280-2.

SEMPLE, B. D., BLOMGREN, K., GIMLIN, K., FERRIERO, D. M. & NOBLE-HAEUSSLEIN, L. J. 2013. Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. Prog Neurobiol, 106-107, 1-16.

SHIBA, K., KAGEYAMA, H., TAKENOYA, F. & SHIODA, S. 2010. Galanin-like peptide and the regulation of feeding behavior and energy metabolism. FEBS J, 277, 5006-13.

SNYDER, E. L. & DOWDY, S. F. 2004. Cell penetrating peptides in drug delivery. Pharm Res, 21, 389-93.

SPETTER, M. S. & HALLSCHMID, M. 2015. Intranasal Neuropeptide Administration To Target the Human Brain in Health and Disease. Mol Pharm, 12, 2767-80.

TALBOT, K., WANG, H. Y., KAZI, H., HAN, L. Y., BAKSHI, K. P., STUCKY, A., FUINO, R. L., KAWAGUCHI, K. R., SAMOYEDNY, A. J., WILSON, R. S., ARVANITAKIS, Z., SCHNEIDER, J. A., WOLF, B. A., BENNETT, D. A., TROJANOWSKI, J. Q. & ARNOLD, S. E. 2012. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J Clin Invest, 122, 1316-38.

THORNE, R. G., PRONK, G. J., PADMANABHAN, V. & FREY, W. H., 2ND 2004. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. Neuroscience, 127, 481-96.

UENO, H., MIZUTA, M., SHIIYA, T., TSUCHIMOCHI, W., NOMA, K., NAKASHIMA, N., FUJIHARA, M. & NAKAZATO, M. 2014. Exploratory trial of intranasal administration of glucagon-like peptide-1 in Japanese patients with type 2 diabetes. Diabetes Care, 37, 2024-7.

VERONESE, F. M. & PASUT, G. 2005. PEGylation, successful approach to drug delivery. Drug Discov Today, 10, 1451-8.

VIVES, E., BRODIN, P. & LEBLEU, B. 1997. A truncated HIV-1 Tat protein basic domain rapidly translocates through the plasma membrane and accumulates in the cell nucleus. J Biol Chem, 272, 16010-7.

WATANABE, Y., MATSUMOTO, Y., KAWAMOTO, K., YAZAWA, S. & MATSUMOTO, M. 1992. Enhancing effect of cyclodextrins on nasal absorption of insulin and its duration in rabbits. Chem Pharm Bull (Tokyo), 40, 3100-4.

ZHANG, H., WU, C., CHEN, Q., CHEN, X., XU, Z., WU, J. & CAI, D. 2013. Treatment of obesity and diabetes using oxytocin or analogs in patients and mouse models. PLoS One, 8, e61477.

Sviatoslav Kharuk. M.Sc. Department of Biochemistry and Biotechnology Vasyl Stefanyk Precarpathian National University, Ivano-Frankivsk, Ukraine;
ORCID ID: 0009-0006-9901-6185

Andrii Shturmak. M.Sc. Department of Biochemistry and Biotechnology Vasyl Stefanyk Precarpathian National University, Ivano-Frankivsk, Ukraine;
ORCID ID: 0009-0008-2893-2789

Volodymyr Shvadchak, Associate Professor, Ph.D., Department of Biochemistry and Biotechnology Vasyl Stefanyk Precarpathian National University, Ivano-Frankivsk, Ukraine;
ORCID ID: 0000-0001-8302-8073

E-mail: sviatoslav.kharuk.19@pnu.edu.ua, andrii.shturmak.19@pnu.edu.ua, volodymyr.shvadchak@pnu.edu.ua

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Харук Святослав, Штурмак Андрій, Швадчак Володимир. ОСТАННІ ДОСЯГНЕННЯ В ІНТРАНАЗАЛЬНІЙ ДОСТАВЦІ ЛІКАРСЬКИХ ПЕПТИДІВ. *Журнал Прикарпатського університету імені Василя Стефаника. Біологія*, **11** (2024), С123–С135.

Лікування нейродегенеративних розладів вимагає доставки ліків у центральну нервову систему. Однак наявність гематоенцефалічного бар'єру (ГЕБ) суттєво обмежує застосування внутрішньовенного та перорального шляхів введення препаратів до мозку. Перспективною, неінвазивною стратегією, що дозволяє обійти ГЕБ і доставити ліки безпосередньо в мозок є інтраназальна доставка. У цьому огляді розглядаються механізми доставки ліків у мозок при введенні через ніс, стратегії покращення та терапевтичні застосування такої доставки, з акцентом на терапевтичні пептиди. Також порівнюються анатомічні відмінності в будові носової порожнини між людьми і модельними тваринами, які використовуються для вивчення ефективності доставки і розглядаються механізми транспортування, включаючи внутрішньоклітинні (аксональні) і позаклітинні (парацелюлярні і трансклітинні) шляхи. Пептидні препарати, схвалені для інтраназального введення, такі як інсулін, ексендин і окситоцин, а також кілька пептидів, що знаходяться на стадії розробки обговорюються більш детально з увагою до впливу амінокислотної послідовності на ефективність доставки. Також, обговорюється нещодавній прогрес у різних стратегіях покращення інтраназальної доставки пептидів, включаючи пегільоване введення, пептиди, що проникають у клітини, та циклодекстрини.

Ключові слова: інтраназальна доставка ліків, гематоенцефалічний бар'єр, введення пептидів, нюховий транспорт, підвищення біодоступності ліків.