

Intranasal insulin – effects on the sense of smell*

Beata Sienkiewicz-Oleszkiewicz^{1,2}, Anna Oleszkiewicz^{2,3}, Maria A. Bock^{2,4}, Thomas Hummel²

Rhinology 61: 5, 404 - 411, 2023

<https://doi.org/10.4193/Rhin23.036>

¹ Department of Clinical Pharmacology, Faculty of Pharmacy, Wrocław Medical University, Poland

² Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany

³ Institute of Psychology, University of Wrocław, Wrocław, Poland

⁴ Departamento de Salud Pública ORL, Hospital General Barrio Obrero, Asunción, Paraguay

*Received for publication:

January 31, 2023

Accepted: July 5, 2023

Abstract

Intranasal insulin (IN) administration is a promising way to deliver the peptide to the central nervous system (CNS), bypassing the blood-brain-barrier and gastrointestinal absorption inhibition. IN receptors are localized in the olfactory mucosa and the brain, mainly in the olfactory bulb, hypothalamus, hippocampus, amygdala, cerebral cortex, and cerebellum. The pleiotropic mechanism of insulin action is characterized by its anti-inflammatory properties, antithrombotic, vasodilatory, and antiapoptotic effects. It prevents energy failure and has regenerative properties, affects neuro-regeneration and counteracts insulin resistance. Hence, insulin has been suggested for various pathological states including neurocognitive disorders, obesity, and as a therapeutic option for smell loss.

A sharply increased prevalence of olfactory dysfunction was observed due to the COVID-19 pandemic. The pandemic also emphasized the lack of therapeutic options for smell loss. Intranasal insulin administration has therefore been suggested to serve as potential treatment, influencing the regenerative capacities of the olfactory mucosa.

This narrative review summarizes current knowledge on possible effects of intranasal insulin on the sense of smell.

Key words: COVID-19, insulin, intranasal administration, obesity, olfaction

Introduction

The sense of smell warns us of potential environmental dangers and it is important for social communication. It is significant for the choice of foods, influences the nutritional status, and energy homeostasis. Without a sense of smell, foods and drinks have no flavour^(1,2).

The sense of smell decreases gradually with aging, and is compromised in various diseases, e.g., diabetes mellitus (DM), Alzheimer's (AD) and Parkinson's Disease⁽³⁻⁵⁾. A sudden loss of the sense of smell is seen, for example, after head trauma or after viral infections of the upper respiratory tract. In SARS-CoV-2 infection smell impairment occurs so often, that smell tests are used to screen for SARS-CoV-2 infections⁽⁶⁾. The overall prevalence of a decreased olfactory function (resulting from infections, head traumas, sinonasal diseases, etc.) in the general population is approximately 20%^(7,8).

Insulin (IN) receptors are present in the olfactory mucosa (OM) the tissue responsible for odour detection. It has been found that IN therapy facilitates the regeneration of olfactory sensory neurons (OSN)⁽⁹⁾. Hence, IN has been listed among the potential

approaches for treatment of smell impairment.

IN was discovered 1921 by Best and Banting⁽¹⁰⁾. Since that time the hormone was of great interest to scientists mainly because of its use in diabetes therapy. As new research emerges, IN is in the spotlight again because of its actions in the central nervous system affecting cognitive functions, influencing neuroprotection and also having an impact on the sense of smell⁽¹¹⁾. IN receptors are mainly localized in the mitral cells of the olfactory bulb and various parts of the brain^(3,12-14). They are also widely distributed in capillaries and small vessel walls influencing the regional perfusion⁽¹⁵⁾. More recent research shows that IN acts not only in neurons but also astrocytes and other types of cells in the brain such as microglia, oligodendrocytes and tanocytes⁽¹⁶⁾. Figure 1 shows selected areas of the central nervous system (CNS) where insulin receptors (IR) are found. Importantly, these areas are also significant for processing olfactory information.

First studies regarding IN focused on its action in peripheral tissues (mainly muscle, liver, and adipose tissue)⁽¹⁶⁾. More recent studies focus on its central action stimulating smell function, ac-

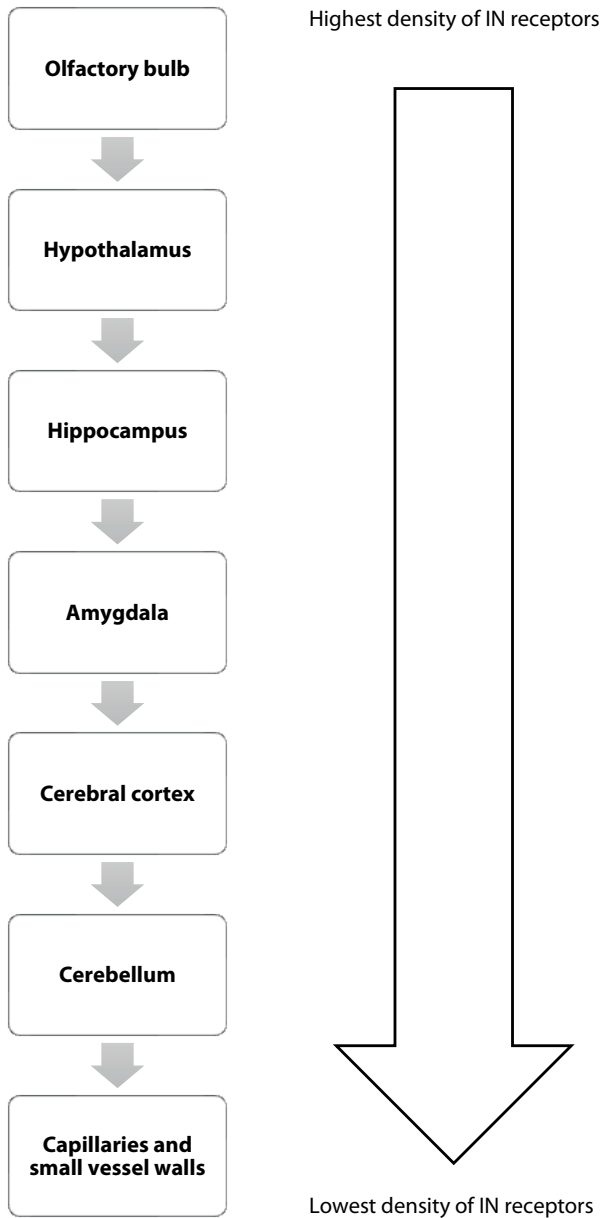


Figure 1. Presence of insulin receptors in the central nervous system.

ting in Alzheimer’s disease and other neurocognitive disorders, even providing neuroprotection in acute ischemic stroke ^(15,17,18). The subcutaneous (SC) way of IN administration is the traditional and most often used one. Nowadays new approaches to deliver IN are being made due to the various disadvantages of SC use and also new scientific data providing evidence that IN might be a therapeutic option in various pathologic conditions, for example, when administered directly to the CNS ^(19,20). One of the more recent methods of IN delivery is the inhalation route. In 2006 the first product for inhalation was approved by the Food and Drug Administration, but later withdrawn from the market by the manufacturer due to low commercial interest. Still, there are other routes of IN administration taken into consideration in clinical trials e.g. oral, oral colon delivery, buccal,

intra-peritoneal, transdermal, and nasal administration ⁽¹⁹⁾.

Intranasal delivery

The intranasal route of insulin administration was first proposed by Frey, who started a series of proof of concept studies in animals, showing that intranasal IN administration allows the peptide to enter the brain without peripheral absorption ⁽¹¹⁾. Studies in humans confirmed that after intranasal administration, IN enters the brain without causing elevation of its peripheral concentration ^(11,21). The intranasal surface area for IN delivery is about 180 cm². The peptide is physiologically secreted into the nasal mucus membrane, where IN-like growth factor (IGF) and IGF receptor 3 are present ⁽²²⁾. Table 1 shows factors influencing intranasally administered IN absorption and possible consequences resulting from changes in the physiological status ^(12,22–24).

The main advantages of intranasal IN delivery relate to the bypassing of gastrointestinal absorption inhibition and the blood-brain barrier (BBB). This enables blood glucose regulation and activation of IN feedback mechanisms directly in the central nervous system ^(22,25,26).

In his review, Benedict et al. showed that intranasal IN delivery can be a promising alternative for the intravenous route of administration, leading to better patient outcomes and avoidance of peripheral side effects connected with that kind of drug administration, especially hypoglycaemia resulting from high doses which would be needed to achieve proper IN concentrations in the CNS ⁽²⁷⁾.

Although the intranasal application route is thought to be a safe way of IN administration, various authors state that progress has to be made to overcome adverse drug reactions related to this administration type, such as nasal irritation (nasal burning, pain, epistaxis) or respiratory symptoms (cough, sinus pain/irritation, coryza) ^(11,28,29). A new approach to overcome this problem is the use of fast dissolving films enabling accurate dosing, rapid IN release, and better application properties ⁽³⁰⁾.

Some studies showed that immediate intranasal administration of IN enhances blood pressure. This effect vanishes with prolonged intranasal administration, which allows the use of intranasal IN in longer (8 weeks) therapies without a significant increase of blood pressure ⁽³¹⁾. Importantly, the elevation of blood pressure as a result of intranasal administration of IN does not exceed normal ranges ⁽³²⁾.

Intranasal IN – potential therapeutic use

Several reviews indicate that intranasal IN may be beneficial to patients undergoing acute ischemic stroke ^(15,33). In this context, intranasal IN has specific neuroprotective qualities including a pleiotropic mechanism of action and a rapid administration route enabling selective cerebral delivery ⁽³³⁾.

Table 1. Factors influencing absorption and bioavailability of intranasally administered insulin.

Factor	Change in physiological status	Consequence
Blood flow	Vasoconstriction	↓ absorption
Mucus	↑ Viscosity	↑ absorption
	pH between 5-6,5	↑ absorption
	↑ mucus production	↓ absorption
	↑ ciliary beat frequency	↓ absorption
Mucociliary membrane	↓ permeability	↓ bioavailability
Enzymes (cytochrome P-450 enzymes, proteases, peptidases)	Possible drug degradation	↓ bioavailability
Macrophages and other immune competent cells	↑ presence	↓ bioavailability
Microbes	↑ presence	↓ bioavailability
Xenobiotics	↑ presence	↓ bioavailability

The pleiotropic mechanism of IN action characterized by its anti-inflammatory properties, antithrombotic and vasodilatory effects, antiapoptotic effect, prevention of energy failure and regenerative properties may be used not only in stroke treatment, but also in neurocognitive impairment therapies, obesity treatment and in acute smell loss management. Molecular mechanisms behind the listed effects are presented in Table 2 (15,34-45).

High density of IN receptors can be found in the hippocampus which is mainly involved in memory organization and cognition (12). Positron emission tomography images provided evidence that changes in brain glucose metabolism may trigger cognition impairments (46). Numerous studies provided evidence that elevation of IN concentration in the CNS leads to memory improvement in various pathological conditions such as Alzheimer’s disease (17,47,48), Parkinson’s disease (4), Down Syndrome (32), and

cognition impairment linked to obesity and DM type 2 (49,50). In 2021 a narrative review highlighted the potentially beneficial role of intranasal IN administration for prevention of delayed neurocognitive recovery and postoperative neurocognitive disorder often reported after hospitalization and connected with anaesthesia, predominantly in cardiac surgery (51). Brünner et al. found that intranasal IN administration improves the delayed odour-cued reactivation of spatial memory in young men. During the study participants were exposed to eight food and non-food odorants. The effect was independent of odour type, and the intranasal IN administration caused no adverse reactions. The authors hypothesized that the use of odours may help maximize the memory-enhancing properties of intranasal IN in cognitively impaired humans (52). In 2004 Hallschmid et al. demonstrated that 8 weeks-long intranasal IN administration (4 x 40 IU/day) to healthy volunteers leads to weight loss and adiposity reduction in men but not in women, suggesting a sex dependency of IN catabolic effect. The investigation gave a promising approach to the therapeutic use of intranasal IN in obesity treatment (53). Later Hallschmid et al. demonstrated in a study with 30 healthy women that postprandially administered intranasal IN enhances the satiating effect of meals and reduces palatable snack intake. Taking into consideration that women are less susceptible to the anorexic effect of IN, the authors hypothesized that the effect could be similar in obese patients, representing general brain IN resistance (54). In line with these conclusions, a study published in 2020 examined sensitivity to a food and a non-food odorant in the hungry and sated state in 75 young healthy (26 normal weight, 25 overweight, and 24 obese) participants. A negative indirect effect of BMI on odour sensitivity for chocolate mediated by the IN resistance was observed (50), corroborating Hallschmid’s hypothesis (54). Furthermore, Rodriguez-Raecke et al. provided evidence that in healthy male subjects gustatory sensitivity was boosted by single dose intranasal IN (40 IU) application. This may also impact food intake, as the detection of the sweet taste

Table 2. Molecular mechanisms behind pleiotropic effects of intranasally administered insulin.

Anti-inflammatory properties	Antithrombotic and vasodilatory effects	Antiapoptotic effect	Prevention of energy failure	Regenerative Properties
↓MMP-9 ↓VEGF ↓TF ↓PAI-1	↓TF ↓PAI-1 ↓ROS ↑eNOS ↑PI-3K/Akt signalling pathway	↑PI-3K/Akt signalling pathway ↓GSK-3β signalling pathway	↑cerebral glucose metabolism ↓neuronal norepinephrine uptake	↑neurite outgrowth ↑regeneration of small myelinated fibres ↑survival of sympathetic and sensory neurons ↑neurotransmission ↑perfusion ↑resting state functional connectivity of the brain

MMP-9: matrix metalloproteinase 9; VEGF: vascular endothelial growth factor; TF: tissue factor; PAI-1: plasminogen activator inhibitor-1; ROS: reactive oxygen species; eNOS: endothelial nitric oxide synthase; PI-3K/Akt: phosphoinositide 3-kinases; GSK-3β: glycogen synthase kinase 3 beta.

was mostly enhanced and the bitter taste less enhanced ⁽⁵⁵⁾. The aforementioned studies suggest that intranasal IN application can be a potential therapeutic option in obesity treatment counteracting IN resistance and contributing to the restoration of chemosensory perception in overweight patients. Another potential target for intranasal IN use is the treatment of acute smell loss, where the smell-restoring effect may result from enhanced regeneration and maturation of OSN after direct IN application to the olfactory epithelium ^(9,15,56,57).

Intranasal IN and normosmia

In 2011 Ketterer et al. aimed to determine whether IN is involved in the regulation of olfactory function. Odour thresholds were measured in 14 healthy subjects eight of which underwent a hyperinsulinemic–euglycemic clamp. In the intervention group, a decrease in odour threshold was observed during euglycemic hyperinsulinemia. In the control group, no such effect was observed after 2h of fasting, indicating that IN regulates the satiation process by reduction of smelling capacity, which is a regulator of food intake ⁽⁵⁸⁾. However, the methodology of this study was invasive and therefore may have led to some biases caused by elevated cortisol levels and altered brain function ⁽²⁹⁾. Since then, several studies were performed to determine the influence of IN on the sense of smell and the possibilities of intranasal IN application, at the same time addressing the caveats of the first study on the effects of intranasal IN administration on olfactory performance.

In a double-blind, placebo-controlled, balanced within-subject study with 17 normal-weight normosmic participants (7 women) Brünner et al. demonstrated that after a single dose of intranasally administered IN (40 IU) the sensitivity for n-butanol decreased significantly, whereas olfactory discrimination ability did not change. After intranasal IN administration neither serum IN nor serum cortisol concentrations were altered. However, a small but significant drop in plasma glucose levels was observed, but it was not related to the effects of intranasal IN on olfactory sensitivity ⁽²⁹⁾.

While these studies in healthy subjects suggested that intranasal IN decreases olfactory sensitivity, results concerning olfactory sensitivity in healthy volunteers according to the gender specificity (similarly to those observed for gustatory sensitivity) are ambiguous. Rodriguez-Raecke et al. demonstrated in a double-blind, placebo-controlled, balanced within-subject study with 30 normal-weight normosmic participants (14 females), that the olfactory sensitivity for n-butanol was lower after intranasal IN administration in women but not in men, as compared to the placebo group. The study was also the first one extending the measures of olfactory sensitivity by utilizing food-related peanut odour, that revealed no significant effects of IN administration ⁽⁵⁹⁾.

Intranasal IN and olfactory disorders

In 2015 Schöpf et al. performed a study among patients with olfactory deficits. Ten anosmic patients received 40 IU of intranasal IN. The study generated different observations than previous ones, performed among healthy volunteers. Two patients presented an immediate increase in odour sensitivity. Odour intensity ratings also increased in a significant manner. Patients with high body mass index (BMI) scores better identified odours immediately after intranasal IN application. Although the observations were the first of their kind, and provided a positive input for further investigations, the study had limitations in terms of the small sample size, lack of randomization and relatively narrow BMI range ⁽³⁾.

In 2018 Rezaeian performed a double-blind randomized controlled clinical trial among 38 hyposmic patients aiming to evaluate the effect of intranasal IN (40 IU) administration on olfactory recovery. After 4 months follow up there was a significant improvement in the n-butanol threshold test in the intervention group, compared to the placebo group. No adverse drug reactions of intranasal IN were observed during the study. The authors therefore suggested intranasal IN administration for the therapeutic management of olfactory dysfunctions ⁽⁶⁰⁾. The study also suffered from a the relatively small sample size and the lack of reference to BMI values. The latter being an important omission as obesity has been shown to reduce the sensitivity to odours via IN resistance ⁽⁵⁰⁾.

Thanarajah et al. performed an investigation to determine the role of peripheral IN sensitivity, reactive blood IN changes and intranasal IN application on olfactory performance in 36 male normal weight and overweight participants. Three different IN doses (40 IU, 100 IU, 160 IU) or corresponding placebo volumes were administered during the test period to each participant. Olfactory threshold and odour discrimination tests were performed and correlated with the homeostasis model assessment of IN resistance. The investigation revealed enhanced odour perception with a dose-dependent improvement of olfactory thresholds after intranasal IN administration, giving more evidence on favourable effects of intranasal IN use in the treatment of olfactory dysfunction. Blood IN and intranasal IN intervention dose influenced olfactory threshold. Higher systemic IN levels correlated negatively with olfactory performance, while higher intranasal IN doses correlated positively with odour sensitivity. The study also showed that it is important to control the fasting state, blood IN levels and peripheral IN sensitivity during intranasal IN testing ⁽¹⁸⁾. Notably, those variables except for blood IN levels were not taken into consideration in previously mentioned studies.

Figure 2 summarizes differences in intranasally administered IN action between healthy individuals and patients with olfactory loss ^(9,58).

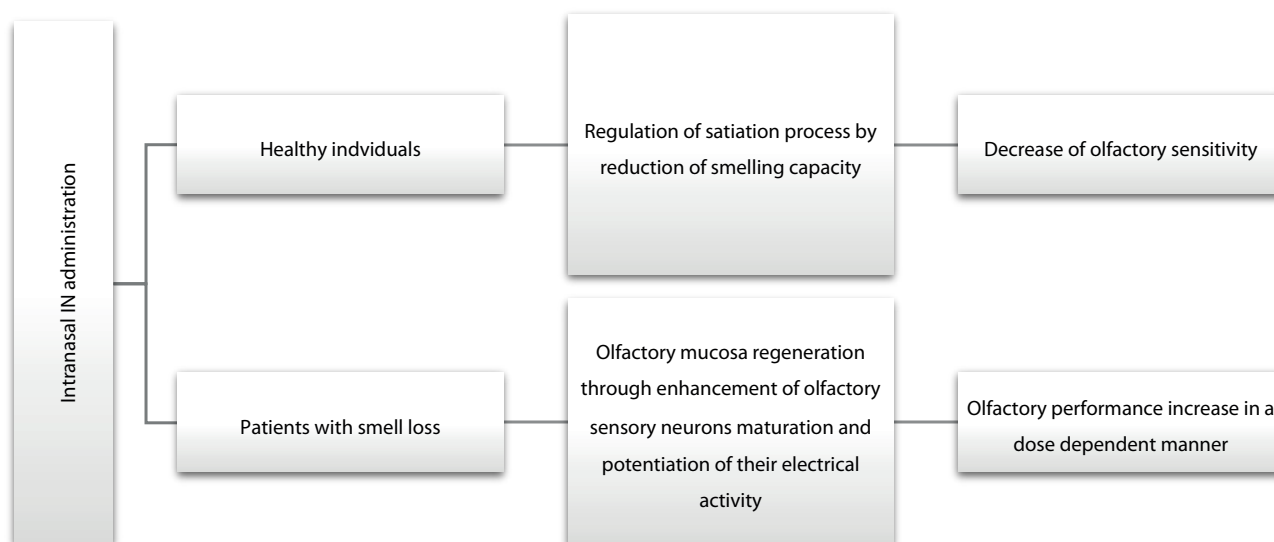


Figure 2. Differences between healthy individuals and patients with olfactory loss in terms of intranasally administered insulin action.

Issues related to studies on insulin effects in olfactory dysfunction

The relatively short intervention time and lack of long-term observations of intranasal IN administration consequences on smell deterioration are among factors limiting the conclusions based on the existing empirical evidence. An additional limitation relates to the relatively short follow-up period which in most studies did not take longer than a year, limiting our knowledge on possible long-term and dose related adverse drug reactions after intranasal IN administration. Most studies were performed using between 20 and 160 IU of insulin during a relatively short period of time ⁽¹¹⁾.

Keeping in mind antiapoptotic effects of insulin action the assumption of potential cancer inducing effects after long-term therapies, may be raised, as the cancer inducing effect of chronic hyperinsulinemia was shown for patients presenting with insulin resistance ⁽⁶¹⁾. To our knowledge no studies on the potential cancer inducing effect of intranasally administered IN were performed to date. In general intranasal insulin administration was found to be safe and well tolerated. After intranasal administration, the peptide was found to inhibit the mitochondrial apoptotic pathway, mainly in mature OSN ⁽⁶²⁾. Therefore it seems not to be very likely that olfactory dysfunction treatment with intranasally administered insulin may induce cancer, although studies with long-term observations are needed to confirm this assumption.

A novel approach to the use of intranasal IN could potentially be related to hyposmia and anosmia caused by the COVID-19 virus. The prevalence of olfactory dysfunction during COVID-19 infection with the delta variant is approximately 40%, varying between different populations and virus strains ⁽⁶³⁾. Although most patients recover from smell loss within 1-3 weeks, some

remain hyposmic or anosmic for months or years ⁽⁶⁴⁾. It is hypothesized that in those patients larger areas of sensory epithelium are affected, possibly with a larger number of lost OSN ^(6,65,66). This group of patients would potentially benefit the most from intranasal IN delivery because IN receptors are also located in sustentacular cells. As stated before IN promotes OM regeneration through the enhancement of newly generated OSN maturation and potentiation of their electrical activity ^(9,56). It is not certain whether globose basal cells express insulin receptors. A study performed by Lacroix et al. confirmed IR in horizontal cells but failed to identify them in globose basal cells due to an aspecific signal during Western blot analysis ⁽⁵⁷⁾. According to Leung et al. and Schwob et al. horizontal basal cells are mainly responsible for the regeneration of the olfactory epithelium after severe injury ^(67,68). In line with this finding stands a study performed by Kikuta et al., demonstrating that higher concentrations of insulin in nasal mucus correlated with preservation of larger amounts of OSN, and indicating a potential protective role of the peptide against olfactory epithelial damage ⁽⁶⁹⁾. On the other hand it has to be kept in mind that globose basal cells also play an important role in the regeneration of olfactory epithelium. Further studies are needed to determine whether IR are present in those cells, because only the activation of horizontal and globose basal cells will allow a complete regeneration of strongly damaged olfactory epithelium.

A recent study aimed to formulate fast dissolving intranasal IN films for the management of COVID-19 associated anosmia. The investigation contained two phases. In the first step films with different composition of hydroxypropyl methyl cellulose and poly vinyl alcohol were prepared and investigated for in vitro characterizations. In the second step a clinical evaluation was performed in 49 participants with post-COVID olfactory loss. The

study was conducted in a single-blinded randomized parallel design. The intervention group received 100 IU IN in the form of a fast-dissolving film twice weekly for four weeks. The placebo group received IN-free films. Thirty minutes after the intervention a significant improvement in olfactory sensitivity and odour discrimination scores in the intervention group was detected⁽³⁰⁾. These results suggest that intranasal IN administration is a promising approach for the treatment of COVID-19-related olfactory loss.

As previously explained insulin may be extracellularly transferred by OSN to the olfactory bulb, which presents high amounts of insulin receptors⁽⁶⁹⁾. Taking into consideration that lower sensory input may lead to atrophy of the OB, intranasal insulin also presents a promising approach to treat the shrunken olfactory bulb in a dual mechanism. First, it protects the olfactory epithelium from injury related OSN loss, what may further preserve a sufficient sensory input. In the second mechanism intranasally administered insulin might support the formation of stable neural circuits by inhibition of OB neuron apoptosis^(69,70). Studies on this topic are needed.

Another field for further investigations are the potential changes of insulin transport to the brain after intranasal application in patients with olfactory dysfunction. Insulin is mainly transported by the extra-neuronal pathway and, as shown in rats, possibly also through the trigeminal nerves^(11,71–73). There are three main mechanisms leading to olfactory loss according to anatomical location of lesion; conductive dysfunction, sensorineural dysfunction, and central dysfunction – these mechanisms are often linked with each other. In fact, pathological conditions often show a combination of different mechanisms. Therefore each pathologic condition with a sensorineural dysfunction, including chronic rhinosinusitis, post-infectious olfactory dysfunction, posttraumatic olfactory dysfunction, and toxin or

medication induced olfactory dysfunction, might potentially change the transport of insulin to the brain after intranasal application⁽⁷⁴⁾. This may impact the treatment outcome of the rapies demanding sufficient insulin concentrations in the CNS after intranasal administration.

Conclusion

Current research indicates that intranasal IN delivery may be a potential therapeutic option in various pathological states. Nasal administration seems to have no adverse effects. Special attention should be paid to the use of intranasal IN in cases of hyposmia, anosmia, and especially in terms of the COVID-associated olfactory loss. The mechanisms behind immediate smell improvement and observation of the long-term consequences of intranasal IN use are fields for further investigations. On the other hand, optimization of intranasal IN administration devices are needed, as there are problems with studies execution and results interpretation for example due to inaccurate dosing^(13,75).

Authorship contribution

All authors contributed to the text of this review, reviewed and approved the final text.

Conflict of interest

Since 2019 TH was supported by the following partners: Sony, Stuttgart, D; Smell and Taste Lab, Geneva, CH; Takasago, Paris, F; aspuracip, Berlin, D; Baia Foods, Madrid, E; Bayer, Berlin, D; Burghart, Holms, D; Primavera, Oy-Mittelberg, D; BSO - Gilead Sciences Poland - Speaker's burea;; AO and MAB declare that they have no conflicts of interest.

Funding

No funding for this review.

References

1. Stevenson RJ. An initial evaluation of the functions of human olfaction. *Chem Senses*. 2009;35(1):3–20.
2. Schäfer L, Schriever VA, Croy I. Human olfactory dysfunction: causes and consequences. *Cell Tissue Res*. 2021;383(1):569–579.
3. Schöpf V, Kollndorfer K, Pollak M, Mueller CA, Freiherr J. Intranasal insulin influences the olfactory performance of patients with smell loss, dependent on the body mass index: A pilot study. *Rhinology*. 2015;53(4):371–378.
4. Novak P, Maldonado DAP, Novak V. Safety and preliminary efficacy of intranasal insulin for cognitive impairment in Parkinson disease and multiple system atrophy: A double-blinded placebo-controlled pilot study. *PLoS One*. 2019;14(4):1–12.
5. Gouveri E, Papanas N. Olfactory dysfunction: A complication of diabetes or a factor that complicates glucose metabolism? a narrative review. *J Clin Med*. 2021;10(23):5637.
6. Butowt R, von Bartheld CS. Anosmia in COVID-19: Underlying Mechanisms and Assessment of an Olfactory Route to Brain Infection. *Neuroscientist*. 2021;27(6):582–603.
7. Desiato VM, Levy DA, Byun YJ, Nguyen SA, Soler ZM, Schlosser RJ. The Prevalence of Olfactory Dysfunction in the General Population: A Systematic Review and Meta-analysis. *Am J Rhinol Allergy*. 2021;35(2):195–205.
8. Pinto JM, Wroblewski KE, Kern DW, Schumm LP, McClintock MK. Olfactory dysfunction predicts 5-year mortality in older adults. *PLoS One*. 2014;9(10):1–9.
9. Kuboki A, Kikuta S, Otori N, et al. Insulin-dependent maturation of newly generated olfactory sensory neurons after injury. *eNeuro*. 2021;8(3):ENEURO.0168-21.2021.
10. Banting F, Best C, Collip J, Campbell W, Fletcher A. Pancreatic extracts in the treatment of diabetes mellitus. *Can Med Assoc J*. 1922;12:141–146.
11. Hallschmid M. Intranasal insulin. *J Neuroendocrinol*. 2021;33(4):1–13.
12. Brünner YF, Benedict C, Freiherr J. Von der Nase ins Gehirn: Effekte intranasal verabreichten Insulins. *Nervenarzt*. 2013;84(8):949–954.
13. de la Monte SM. Intranasal insulin therapy for cognitive impairment and neurodegeneration: current state of the art. *Expert Opin Drug Deliv*. 2013;10(12):1699–1709.
14. Fadool DA, Tucker K, Pedarzani P. Mitral cells of the olfactory bulb perform metabolic sensing and are disrupted by obesity at the level of the Kv1.3 ion channel. *PLoS One*. 2011;6(9):10–12.
15. Lioutas VA, Alfaro-Martinez F, Bedoya F,

- Chung CC, Pimentel DA, Novak V. Intranasal Insulin and Insulin-Like Growth Factor 1 as Neuroprotectants in Acute Ischemic Stroke. *Transl Stroke Res.* 2015;6(4):264–275.
16. González-García I, Gruber T, García-Cáceres C. Insulin action on astrocytes: From energy homeostasis to behaviour. *J Neuroendocrinol.* 2021;33(4):1–11.
 17. Avgerinos KI, Kalaitzidis G, Malli A, Kalaitzoglou D, Myserlis PG, Lioutas V. Intranasal insulin in Alzheimer's dementia or mild cognitive impairment: a systematic review. *J Neurol.* 2018;265(7):1497–1510.
 18. Edwin Thanarajah S, Hoffstall V, Rigoux L, Hanssen R, Brüning JC, Tittgemeyer M. The role of insulin sensitivity and intranasally applied insulin on olfactory perception. *Sci Rep.* 2019;9(1):1–8.
 19. Shah R, Patel M, Maahs D, Shah V. Insulin delivery methods: Past, present and future. *Int J Pharm Investig.* 2016;6(1):1–9.
 20. Summary of Product Characteristics Actrapid Penfill. https://www.ema.europa.eu/en/documents/product-information/actrapid-epar-product-information_en.pdf Accessed: 04.01.2023.
 21. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL. Sniffing neuropeptides: a transnasal approach to the human brain. *Nat Neurosci.* 2002;5(6):514–516.
 22. Henkin RI. Inhaled insulin-Intrapulmonary, intranasal, and other routes of administration: Mechanisms of action. *Nutrition.* 2010;26(1):33–39.
 23. Pires A, Fortuna A, Alves G, Falcão A. Intranasal drug delivery: How, why and what for? *J Pharm Pharm Sci.* 2009;12(3):288–311.
 24. Illum L. Nasal drug delivery - Possibilities, problems and solutions. *J Control Release.* 2003;87(1–3):187–198.
 25. Kern W, Born J, Schreiber H, Fehm HL. Central nervous system effects of intranasally administered insulin during euglycemia in men. *Diabetes.* 1999;48(3):557–563.
 26. Sigurdsson P, Thorvaldsson T, Gizurarson S, Gunnarsson E. Olfactory absorption of insulin to the brain. *Drug Deliv J Deliv Target Ther Agents.* 1997;4(3):195–200.
 27. Benedict C, Frey WH, Schiöth HB, Schultes B, Born J, Hallschmid M. Intranasal insulin as a therapeutic option in the treatment of cognitive impairments. *Exp Gerontol.* 2011;46(2–3):112–115.
 28. Owens DR, Zinman B, Bolli G. Alternative routes of insulin delivery. *Diabet Med.* 2003;20(11):886–898.
 29. Brünner YF, Benedict C, Freiherr J. Intranasal insulin reduces olfactory sensitivity in normosmic humans. *J Clin Endocrinol Metab.* 2013;98(10):1626–1630.
 30. Mohamad SA, Badawi AM, Mansour HF. Insulin fast-dissolving film for intranasal delivery via olfactory region, a promising approach for the treatment of anosmia in COVID-19 patients: Design, in-vitro characterization and clinical evaluation. *Int J Pharm.* 2021;601.120600.
 31. Benedict C, Dodt C, Hallschmid M, et al. Immediate but not long-term intranasal administration of insulin raises blood pressure in human beings. *Metabolism.* 2005;54(10):1356–1361.
 32. Rosenbloom M, Barclay T, Johnsen J, et al. Double-Blind Placebo-Controlled Pilot Investigation of the Safety of a Single Dose of Rapid-Acting Intranasal Insulin in Down Syndrome. *Drugs R D.* 2020;20(1):11–15.
 33. Lioutas VA, Novak V. Intranasal insulin neuroprotection in ischemic stroke. *Neural Regen Res.* 2016;11(3):400–401.
 34. Philpott KL, McCarthy MJ, Klippel A, Rubin LL. Activated phosphatidylinositol 3-kinase and Akt kinase promote survival of superior cervical neurons. *J Cell Biol.* 1997;139(3):809–815.
 35. Dandona P, Aljada A, Mohanty P, Ghanim H, Bandyopadhyay A, Chaudhuri A. Insulin suppresses plasma concentration of vascular endothelial growth factor and matrix metalloproteinase-9. *Diabetes Care.* 2003;26(12):3310–3314.
 36. Aljada A, Ghanim H, Mohanty P, Kapur N, Dandona P. Insulin inhibits the pro-inflammatory transcription factor early growth response gene-1 (Egr)-1 expression in mononuclear cells (MNC) and reduces plasma tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) concentrations. *J Clin Endocrinol Metab.* 2002;87(3):1419–1422.
 37. White MF, Kahn CR. Insulin action at a molecular level – 100 years of progress. *Mol Metab.* 2021;52:101304.
 38. Dimmeler S, Fleming I, Fisslthaler B, Hermann C, Busse R, Zeiher AM. Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation. *Nature.* 1999;399(6736):601–605.
 39. Duarte AI, Santos P, Oliveira CR, Santos MS, Rego AC. Insulin neuroprotection against oxidative stress is mediated by Akt and GSK-3 β signaling pathways and changes in protein expression. *Biochim Biophys Acta - Mol Cell Res.* 2008;1783(6):994–1002.
 40. Schulingkamp RJ, Pagano TC, Hung D, Raffa RB. Insulin receptors and insulin action in the brain: Review and clinical implications. *Neurosci Biobehav Rev.* 2000;24(8):855–872.
 41. Duarte AI, Moreira PI, Oliveira CR. Insulin in central nervous system: More than just a peripheral hormone. *J Aging Res.* 2012;2012.
 42. Recio-Pinto E, Rechler MM, Ishii DN. Effects of insulin, insulin-like growth factor-II, and nerve growth factor on neurite formation and survival cultured sympathetic and sensory neurons. *J Neurosci.* 1986;6(5):1211–1219.
 43. Novak V, Milberg W, Hao Y, et al. Enhancement of vasoreactivity and cognition by intranasal insulin in Type 2 diabetes. *Diabetes Care.* 2014;37(3):751–759.
 44. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnesic mild cognitive impairment: A pilot clinical trial. *Arch Neurol.* 2012;69(1):29–38.
 45. Zhang H, Hao Y, Manor B, et al. Intranasal insulin enhanced resting-state functional connectivity of hippocampal regions in type 2 diabetes. *Diabetes.* 2015;64(3):1025–1034.
 46. Mosconi L, Mistur R, Switalski R, et al. FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease. *Eur J Nucl Med Mol Imaging.* 2009;36(5):811–822.
 47. Benedict C, Hallschmid M, Schultes B, Born J, Kern W. Intranasal insulin to improve memory function in humans. *Neuroendocrinology.* 2007;86(2):136–142.
 48. Messier C, Teutenberg K. The role of insulin, insulin growth factor, and insulin-degrading enzyme in brain aging and Alzheimer's disease. *Neural Plast.* 2005;12(4):311–328.
 49. Zhang Z, Zhang B, Wang X, et al. Olfactory dysfunction mediates adiposity in cognitive impairment of type 2 diabetes: Insights from clinical and functional neuroimaging studies. *Diabetes Care.* 2019;42(7):1274–1283.
 50. Poessel M, Freiherr J, Wiencke K, Villringer A, Horstmann A. Insulin resistance is associated with reduced food odor sensitivity across a wide range of body weights. *Nutrients.* 2020;12(8):1–16.
 51. Badenes R, Qeva E, Giordano G, Romero-García N, Bilotta F. Intranasal insulin administration to prevent delayed neurocognitive recovery and postoperative neurocognitive disorder: A narrative review. *Int J Environ Res Public Health.* 2021;18(5):1–13.
 52. Brünner YF, Kofoet A, Benedict C, Freiherr J. Central insulin administration improves odor-cued reactivation of spatial memory in young men. *J Clin Endocrinol Metab.* 2015;100(1):212–219.
 53. Hallschmid M, Benedict C, Schultes B, Fehm HL, Born J, Kern W. Intranasal insulin reduces body fat in men but not in women. *Diabetes.* 2004;53(11):3024–3029.
 54. Hallschmid M, Higgs S, Thienel M, Ott V, Lehnert H. Postprandial administration of intranasal insulin intensifies satiety and reduces intake of palatable snacks in women. *Diabetes.* 2012;61(4):782–789.
 55. Rodríguez-Raecke R, Yang H, Bruenner YF, Freiherr J. Intranasal Insulin Boosts Gustatory Sensitivity. *J Neuroendocrinol.* 2017;29(1).
 56. Savigner A, Duchamp-Viret P, Grosmaître X, et al. Modulation of spontaneous and odorant-evoked activity of rat olfactory sensory neurons by two anorectic peptides, insulin and leptin. *J Neurophysiol.* 2009;101(6):2898–2906.
 57. Lacroix MC, Badonnel K, Meunier N, et al. Expression of insulin system in the olfactory epithelium: First approaches to its role and regulation. *J Neuroendocrinol.* 2008;20(10):1176–1190.
 58. Ketterer C, Heni M, Thamer C, Herzberg-Schäfer SA, Häring H-U, Fritsche A. Acute, short-term hyperinsulinemia increases olfactory threshold in healthy subjects. *Int J Obes.* 2011;35(8):1135–1138.
 59. Rodríguez-Raecke R, Brünner YF, Kofoet A, Mutic S, Benedict C, Freiherr J. Odor sen-

- sitivity after intranasal insulin application is modulated by gender. *Front Endocrinol (Lausanne)*. 2018;9:1–8.
60. Rezaeian A. Effect of Intranasal Insulin on Olfactory Recovery in Patients with Hyposmia: A Randomized Clinical Trial. *Otolaryngol - Head Neck Surg (United States)*. 2018;158(6):1134–1139.
 61. Arcidiacono B, Iiritano S, Nocera A, et al. Insulin resistance and cancer risk: An overview of the pathogenetic mechanisms. *Exp Diabetes Res*. 2012;2012:789174.
 62. Lacroix MC, Rodriguez-Enfedaque A, Grébert D, et al. Insulin But Not Leptin Protects Olfactory Mucosa From Apoptosis. *J Neuroendocrinol*. 2011;23(7):627–640.
 63. Von Bartheld CS, Butowt R, Hagen MM. Prevalence of chemosensory dysfunction in COVID-19 patients: A systematic review and meta-analysis reveals significant ethnic differences. *ACS Chem Neurosci*. 2020;11(19):2944–2961.
 64. Tan BKJ, Han R, Zhao JJ, et al. Prognosis and persistence of smell and taste dysfunction in patients with covid-19: Meta-analysis with parametric cure modelling of recovery curves. *BMJ*. 2022;1–12.
 65. Khan M, Yoo S-J, Clijsters M, et al. Visualizing in deceased COVID-19 patients how SARS-CoV-2 attacks the respiratory and olfactory mucosae but spares the olfactory bulb. *Cell*. 2021;184(24):5932–5949.e15.
 66. Finlay JB, Brann DH, Abi Hachem R, et al. Persistent post-COVID-19 smell loss is associated with immune cell infiltration and altered gene expression in olfactory epithelium. *Sci Transl Med*. 2022;14(676):eadd0484.
 67. Leung CT, Coulombe PA, Reed RR. Contribution of olfactory neural stem cells to tissue maintenance and regeneration. *Nat Neurosci*. 2007;10(6):720–726.
 68. Schwob JE, Jang W, Holbrook EH, et al. Stem and progenitor cells of the mammalian olfactory epithelium: Taking poietic license. *J Comp Neurol*. 2017;525(4):1034–1054.
 69. Kikuta S, Kuboki A, Yamasoba T. Protective Effect of Insulin in Mouse Nasal Mucus Against Olfactory Epithelium Injury. *Front Neural Circuits*. 2021;15:1–11.
 70. Patterson A, Hähner A, Kitzler HH, Hummel T. Are small olfactory bulbs a risk for olfactory loss following an upper respiratory tract infection? *Eur Arch Oto-Rhino-Laryngology*. 2015;272(11):3593–3594.
 71. Lochhead JJ, Kellohen KL, Ronaldson PT, Davis TP. Distribution of insulin in trigeminal nerve and brain after intranasal administration. *Sci Rep*. 2019;9(1):1–9.
 72. Borrajo ML, Alonso MJ. Using nanotechnology to deliver biomolecules from nose to brain — peptides, proteins, monoclonal antibodies and RNA. *Drug Deliv Transl Res*. 2022;12(4):862–880.
 73. Lee D, Minko T. Nanotherapeutics for nose-to-brain drug delivery: An approach to bypass the blood brain barrier. *Pharmaceutics*. 2021;13,2049.
 74. Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. *Rhinology*. 2017;54:1–30.
 75. Craft S, Raman R, Chow TW, et al. Safety, Efficacy, and Feasibility of Intranasal Insulin for the Treatment of Mild Cognitive Impairment and Alzheimer Disease Dementia: A Randomized Clinical Trial. *JAMA Neurol*. 2020;77(9):1099–1109.

Beata Sienkiewicz-Oleszkiewicz
 Department of Clinical Pharmacology
 Faculty of Pharmacy
 Wrocław Medical University
 Poland

E-mail:
 beata.sienkiewicz-oleszkiewicz@
 umw.edu.pl