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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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THE EFFECT OF INTRANASAL ADMINISTRATION OF BIOLOGICALLY ACTIVE SUBSTANCES OF AMINO ACID AND PEPTIDE NATURE ON THE MONOAMINE SYSTEMS OF THE BRAIN

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Abstract.

Introduction: The annual growth of psychiatric and neurodegenerative diseases requires new therapeutic strategies for delivering active pharmaceutical molecules to the brain. Non-invasive intranasal drug delivery is a promising method that allows bypassing of the blood-brain barrier and the liver de-toxification system.

Results: The review discusses the main results of experimental studies of the effect of intranasal substances of amino acid and peptide nature on the monoamine systems of the brain. The main attention is paid to understanding the transport mechanisms of potential amino acid and peptide drugs in the nose-to-brain projection and assessing their therapeutic efficacy.

Conclusion: The obtained results indicate the possibility of creating, along with buccal, in-halation, transdermal and ocular preparations, intranasal non-invasive drugs that provide more effective therapy for psychiatric and neurodegenerative diseases, such as schizophrenia, depression, anxiety, ADHD, Alzheimer disease and Parkinson disease.

Key words. Intranasal administration, Nose-to-brain projection, Psychiatric/neurodegenerative diseases, non-invasive drugs, peptides, insulin, levodopa, amino acids, monoamine systems.

Introduction.

Currently, numerous animal and human studies have shown that amino acids and peptides are among the most promising with minimal toxicity.

A non-invasive intranasal route of drug delivery is to the central nervous system, allowing it to bypass the blood-brain barrier and the liver detoxification system. Animal models are indispensable for preclinical drug testing, offering valuable information on absorption efficiency and potential variables affecting the formulation`s safety.

The presented ideas aim to guide future research in intranasal drug delivery in neurological disorders, providing more accurate predictions of therapeutic efficacy in clinical settings [1]. To date, a large body of data has been acquired to the study of the olfactory system. For example, the activity of neurons in various areas of the brain, including the olfactory cortex, amygdala, ento-rhinal cortex, and hippocampus, has been well studied, resulting in the identification of brain regions that perform different functions in the analysis of odor information [2]. Understanding the neural mechanisms of olfaction may help in the development of new treatments for many neuro-logical diseases, such as Alzheimer's or Parkinson's disease.

Providing non-invasive delivery of proteins across mucosal barriers promises to improve patient compliance and treatment efficacy. Cell-penetrating peptides (CPPs) are emerging as a promising and versatile tool to enhance the penetration of proteins and peptides across various mucosal barriers. Recent developments in CPPs to overcome mucosal barriers for protein delivery are summarized and analyzed. Perspectives on current challenges and future research directions aimed at improving non-invasive transmucosal delivery of macromolecules for ultimate clinical translation are discussed [3].

Animal and human studies have shown that oxytocin (OT) administered intranasally can penetrate the brain and induce cognitive, emotional, and behavioral changes, particularly in social functioning. According to Yin et al., some data on the effect of intranasal oxytocin on anxiety and autism are contradictory [4].

Insulin is a key pharmacological target in the fight against diabetes. Subcutaneous insulin administration has several limitations and disadvantages. In this regard, the development of alternative methods of insulin administration is relevant. These include buccal, oral, inhalation, transdermal, ocular, vaginal, rectal and intranasal routes. Researchers are faced with the task of finding a safe non-invasive method of insulin delivery with a high level of absorption and bioavailability. Advanced micro/nanocomposite technologies are being developed to implement new insulin delivery routes [5]. In addition to the peripheral action of insulin on organs and tissues, its effects on the central nervous system are of great importance. Because intranasal insulin delivery helps to overcome limiting factors such as the blood-brain barrier and does not lead to systemic hypoglycemia, this method is the most promising for studying the central action of insulin. To date, many interesting studies have been conducted examining the central effects of intranasal insulin, including its impact on the course of neurodegenerative diseases in patients and animal models. Due to the large amount of information available, we have dedicated a separate chapter to intranasal insulin in our review [5].

Intranasal insulin administration has potential for the treatment of Alzheimer's disease (AD). The relationship between AD and diabetes mellitus has been suggested and studied. Notably, intranasal insulin exerts neuroprotective effects by influencing Aβ clearance, tau phosphorylation, and synaptic plasticity. In preclinical studies and clinical trials, intranasally administered insulin achieved rapid and extensive distribution throughout the brain, with optimal formulations demonstrating minimal systemic circulation. Despite the promising prospects, challenges remain in the delivery of protein drugs from the nasal cavity to the brain, including enzymes, tight junctions, mucociliary clearance, and precise drug deposition, which hinder its translation into the clinical setting.

Future studies should address issues related to drug absorption, nasal deposition, and long-term effects of intranasal insulin administration [6].

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by the accumulation of neurofibrillary tangles and β-amyloid plaques. Recent studies have uncovered a key role for dysfunctional insulin signaling in the pathogenesis of AD. Insulin once thought to be unrelated to brain function, has emerged as a critical factor in neuronal survival, synaptic plasticity, and cognitive processes. Insulin and its downstream insulin signaling molecules are found primarily in the hippocampus and cerebral cortex. Some of the molecules responsible for dysfunctional insulin signaling include GSK-3β, Akt, PI3K, and IRS. This, in turn, is considered a crucial factor contributing to the development of AD, which is characterized by oxidative stress, neuroinflammation, and other pathological hallmarks. Moreover, this pathway is indirectly influenced by Nrf2, NF-κB, and caspases.

Innovative approaches involving the use of nanoparticles and intranasal insulin delivery may potentially reduce the effect of insulin resistance on the development of Alzheimer's disease [7]. Due to their high target specificity and low toxicity, biologics have been successfully applied in a wide range of therapeutic areas. It should also be noted that biologics have unfavorable pharmacokinetic properties, are susceptible to degradation by endogenous enzymes, and cannot penetrate biological barriers such as the blood-brain barrier (i.e., the main obstacle to reaching the central nervous system (CNS)). Attempts to overcome these problems have been made by using the intracerebroventricular and intrathecal routes of administration. However, the invasiveness and im-practicality of these procedures have prompted the development of new drug delivery strategies, including the intranasal route. This represents a non-invasive route to target the CNS that reduces systemic exposure. To maximize the benefits of the intranasal route, new approaches have been proposed, including the use of cell-penetrating peptides (CPPs) and CPP-functionalized nanosystems [8].

Nasal mucosal peptide drugs such as insulin and calcitonin have been widely used in the medical field. There are always two sides to a coin. On the one hand, intranasal drug delivery can mimic the secretion structure in the human body, having the advantages of physiological structure and ease of use. On the other hand, the low permeability of the nasal mucosa, protease environment, and clearance effect of nasal cilia hinder the intranasal absorption of peptide drugs. Re-searchers have used several methods to achieve faster therapeutic concentration, lower treatment dose, and fewer side effects to improve nasal drugs. As a result, absorption enhancers, nanoparticles (NPs), and bioadhesive systems are the most widely used. Among them, chitosan (CS), cell-penetrating peptides (CPPs), tight junction modulators (TJMs), soft nanoparticles, and gel/hydrogel are the most promising strategies. Moreover, two or three strategies can be combined to obtain drug vectors. In addition, spray freeze-drying (SFD), self-emulsifying nanosystem (SEN), and glucose-responsive intelligent drug delivery systems will be new research directions in the future [9].

Depression and anxiety are common and debilitating mental disorders that are usually treated with antidepressants or anxiolytics, respectively. However, the treatment is usually administered orally, but the low permeability of the blood-brain barrier reduces the amount of drug that can reach it, which consequently reduces the therapeutic efficacy. That is why it is of utmost importance to find new solutions that will make these treatments more effective, safer, and faster. Results from pharmacokinetic and pharmacodynamic studies in vivo have shown that intranasal administration may be more effective in targeting the brain than other routes of administration. These strategies may be key to future improved treatments for depressive and anxiety disorders [10].

The proposed transnasal mechanisms of nose-to-brain transport of potential amino acid and peptide drugs are shown in Figure 1.

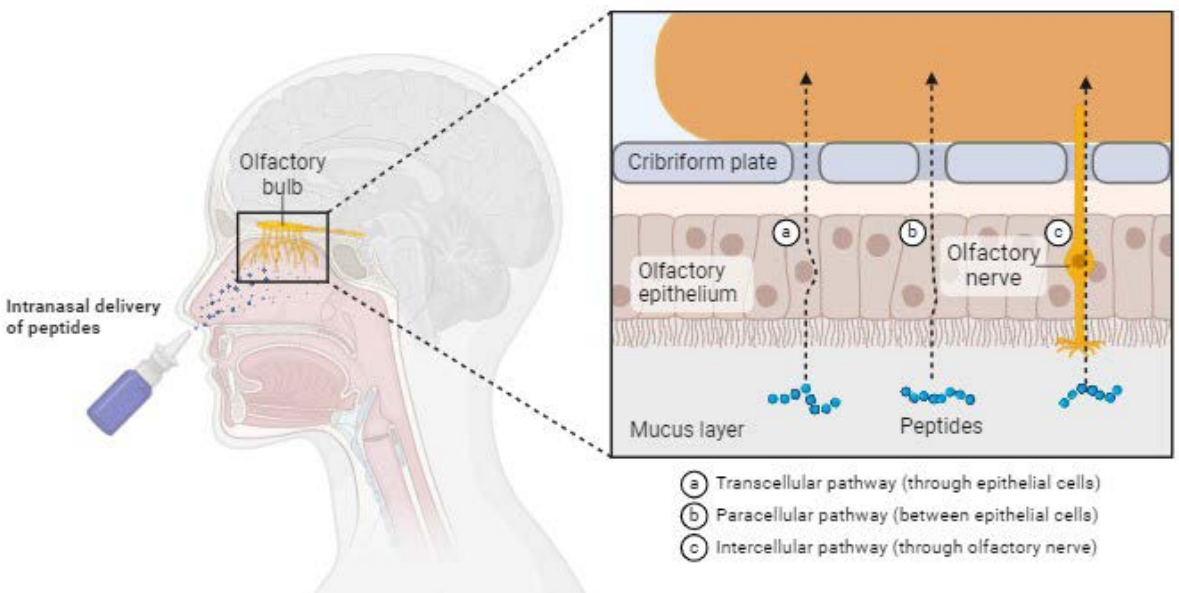

Figure 1. *Transnasal mechanisms of amino acid and peptide nature potential drugs transport in the nose-to-brain projection.*

Insulin.

Insulin intranasal administration and metabolic diseases:

Insulin is a protein hormone that can affect the central nervous system. Insulin can cause metabolic and behavioral changes.

In response to intranasal insulin administration in people with normal and overweight weight, a decrease in cerebral blood flow (CBF) in the prefrontal cortex was found only in lean participants. At the same time, cerebral blood flow in the hypothalamus in response to intranasal insulin de-creased in all participants, but to a greater extent in lean people. The authors demonstrate a relationship between a decrease in peripheral and central insulin tolerance in obesity and the associated changes in eating behavior that contribute to overeating [11].

A connection between type 2 diabetes mellitus and CNS insulin resistance and the development of Alzheimer's disease has been shown. Possible mechanisms for the connection between glucose metabolism disorders and AD may be associated with desensitization of insulin signaling in the brain in obesity and T2DM, impaired insulin function in the CNS, and decreased sensitivity of insulin receptors [6].

Modulation of dopaminergic transmission via insulin intranasal administration.

Insulin receptors are expressed in all parts of the brain. The dopaminergic system, in particular the mesolimbic dopamine system, which is involved in motivation and reinforcement of eating behavior, is recognized as an important target of insulin [12]. After intranasal insulin administration, synaptic insulin levels were assessed using $^{[11C]}$raclopride (a dopamine D2/3 receptor ligand) positron emission tomography and resting-state functional MRI. A greater $^{[11C]}$raclopride binding potential was observed in the bi-lateral ventral and dorsal striatum after insulin administration compared to placebo, suggesting an insulin-induced decrease in synaptic dopamine levels [13].

The findings of Thanarajah et al. using fMRI data after intranasal insulin administration, are consistent with the idea that insulin regulates feeding behavior through its effects on midbrain dopaminergic neurons, influencing reward and motivation processes [14]. In a mouse study, intranasal insulin demonstrated suppression of cocaine-induced locomotor activity, while suppression was not observed in the presence of the insulin receptor antagonist S961 [15]. Acute hypoxic-ischemic encephalopathy (HIE) of neonates is a severe complication of birth asphyxia.

Insulin intranasal administration and neurobehavioral dysfunction.

That find approaches that third of these conditions, that effect of intranasal insulin he still-mia-induced neurobehavioral dysfunction you studied in neonatal rats.

Intranasal insulin reduced sensorimotor behavioral impairments in the tests for the righting reflex, negative geotaxis, wire suspension maneuver, hindlimb suspension, and ipsilateral damage in the immunohistochemical examination of brain tissue [16]. Phelan-McDermid syndrome (PMS) is a rare genetic disorder caused by a deletion of 22q13.3. The syndrome is clinically characterized by mental retardation and behavioral disorders of the autism spectrum [17]. Zwanenburg et al. conducted a randomized, double-blind, placebo-controlled clinical trial in which intranasal insulin spray administered daily for 6 months resulted in improved cognitive and social skills in children with PMS over the age of three [18].

A randomized, double-blind, placebo-controlled study of the therapeutic effect of intranasal insulin was conducted in adults with bipolar disorder in a euthymic state. After intranasal administration of 40 IU insulin four times a day for eight weeks, the control group showed a significant improvement in executive function compared to placebo in neurocognitive testing [19].

The effect of intranasal insulin on the hypothalamic-pituitary-adrenal (HPA) axis under stress conditions was studied. In a study on young healthy men, intranasal insulin at a dose of 40 IU, administered 50 minutes before the Trier Social Stress Test (TSST), significantly reduced the increase in salivary and plasma cortisol levels compared to placebo, without changing heart rate and blood pressure [20].

Insulin intranasal administration and neurodegenerative diseases.

A connection between type 2 diabetes mellitus and CNS insulin resistance and the development of Alzheimer's disease (AD) has been shown, in connection with which the development of therapy aimed at normalizing insulin signaling in the brain in AD may be promising [21]. Possible mechanisms for the connection between glucose metabolism disorders and AD may be associated with desensitization of insulin signaling in the brain in obesity and T2DM, impaired insulin function in the CNS, and decreased sensitivity of insulin receptors [6]. In studies on an animal model of Alzheimer's disease (APPswe/PS1dE9 transgenic mice), 6-week administration of intranasal insulin led to a decrease in cognitive deficit, a decrease in b-amyloid production and plaque formation due to a decrease in amyloidogenic processing of the APP protein (a b-amyloid precursor) and a decrease in the content of apolipoprotein E in the brain of mice [22]. Intranasal insulin administration at a dose of 2 U/day for 6 weeks restored cerebral glucose metabolism in the prefrontal and cingulate cortex, and attenuated astroglial activation and neuronal death in the hippocampus in rats with streptozotocin injection-induced AD (ICV-STZ) [23]. Clinical studies of intranasal insulin have demonstrated a better effect on improving cognitive abilities and verbal memory in patients with AD and amnestic mild cognitive impairment (MCI) who do not have the APOE-epsilon4 allele (APOE- ε4 -) [24,25].

The study by Rosenbloom et al. 2008 demonstrated good tolerability of intranasal rap-id-acting insulin glulisine in 9 patients with mild to moderate AD who had the *ApoE4* gene but did not reveal a significant effect on cognitive functions [26]. Intranasal administration of insulin resulted in improvement of delayed verbal memory and preservation of general cognitive abilities, assessed by the ADAS-cog scale, and the ability to perform daily functions [27]. A more recent study demonstrated differential effects of intranasal insulin in patients with MCI and AD de-pending on gender and *ApoE* ε4 status. All participants showed cognitive improvement with 20 IU/day of intranasal insulin for 4 months, but only men showed this effect with 40 IU/day. At the 40 IU dose, *ApoE* ε4-negative men showed improvement, while ApoE ε4-negative women showed

deterioration. *ApoE* ε4-positive patients remained cognitively stable [28]. In a study of intranasal administration of detemir (long-acting intranasal insulin) for 21 days at a dose of 40 IU, *ApoE* ε4-positive patients showed improvement in verbal memory and visuospatial working memory, while *ApoE* ε4-negative patients showed deterioration, which distinguishes the treatment results about the presence of the *ApoE* ε4 gene from previous studies that used short-acting insulin [29]. In another study, intranasal insulin use in patients with MCI and AD for 12 months resulted in a decrease in white matter hyperintensities (WMH) as measured by magnetic resonance imaging [30]. Increased WMH correlates with worsening of the AD-CSF biomarker profile (Aβ to tau ratio) and cognitive performance [30,31].

It was shown the effect of intranasal insulin administration on cognitive and functional outcomes in adults with Alzheimer's disease [27,32]. The results showed an improvement in delayed memory compared to placebo. The effects of intranasal insulin were studied in 5xFAD transgenic mice, a model of Alzheimer's disease. The mice showed a dose-dependent increase in grip strength in the wire hang test, a decrease in frailty, and an increase in swimming speed and visual-spatial memory in the Morris water maze [33].

There is evidence for the possibility of using intranasal insulin in Parkinson's disease. The study by Novak et al. involved 16 patients with Parkinson's disease, 8 of whom received 40 IU of insulin intranasally for four weeks [34]. After treatment, the group receiving intranasal insulin had a better overall score on the FAS (verbal fluency) test compared to the placebo group and also showed an improvement in the Hoehn and Yahr (HY) scale from baseline.

Thus, intranasal administration is a promising method of delivering the peptide hormone insulin to the brain for the effective treatment of neurodegenerative and metabolic diseases.

Levodopa (3-Hydroxy-L-tyrosine).

Parkinson's disease (PD) is a neurodegenerative disorder in which the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) of the midbrain results in dopamine deficiency. Levodopa (L-DOPA) is the mainstay and most effective drug for the treatment of Parkinson's disease. Following systemic absorption, levodopa can cross the BBB and reach the brain where it can be converted to dopamine by aromatic L-amino acid decarboxylase (AAAD), also known as DOPA decarboxylase (DDC), at the presynaptic terminals of dopaminergic neurons [35].

This drug is often administered orally, but its bioavailability is relatively low, reducing the therapeutic effect while still allowing for symptom progression [36,37]. Oral levodopa requires a continuous increase in dosage as PD progresses and dopaminergic neurons die. With a large in-crease in dosage, an "ON-OFF" phenotype develops, when there are strong fluctuations in dopa-mine levels between courses of treatment, which leads to pronounced side effects such as dyskinesia [38]. The intranasal route of administration of drugs, including levodopa, has several advantages, including non-invasiveness, overcoming the blood-brain barrier, preventing elimination of the drug during passage through the liver, and a decrease in systemic side effects associated with the decarboxylation of L-DOPA in peripheral tissues [39]. Levodopa molecules in a liquid medium are unstable and prone to oxidation, as a result of it is better to use a powder form for intranasal delivery of levodopa [36]. Levodopa in powder form has good physical and chemical stability, which contributes to better-controlled release to achieve maximum therapeutic efficacy [40]. A study by Xuan Liu et al. compared the efficacy of intranasal delivery of levodopa in powder form with different microparticle sizes ranging from 36.92 to 45.70 μm in diameter and excipients: hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP) or hydroxypropyl-β-cyclodextrin (CD) [35]. A promising direction in the development of an intranasal form of L-DOPA is encapsulation in polymer- and lipid-based nanoparticles. These formulations can protect L-DOPA from systemic decarboxylation to dopamine and improve the delivery of L-DOPA to the central nervous system [41]. Thus, levodopa was shown to form stable 300 nm nanoparticles when encapsulated in N-palmitoyl-N-monomethyl-N,N-dimethyl-N,N,N-trimethyl-6-O-glycol chitosan (GCPQ). Nasal administration of reconstituted GCPQ-L-DOPA nanoparticles to rats resulted in a significant increase in brain dopamine levels, but not in peripheral plasma, compared to pure L-DOPA [42].

Organic nanoparticles can be modified to further enhance their ability to cross the blood-brain barrier, for example, by altering the surface charge and hydrophobicity of the particles [43]. In addition, organic nanoparticles can be modified with ligands [44]. Such ligands include antibodies, peptides, and proteins located on the surface of the NPs, which provide specific interaction with BBB cell receptors, such as transferrin receptors, insulin receptors, leptin receptors, low-density lipoprotein receptors, and lactoferrin receptors [41,45].

Intranasal administration of L-DOPA-containing nanoparticles avoids the interfering effect of the blood-brain barrier. The small size of nanoparticles allows for faster delivery of the substance to the brain via the extracellular mechanism along the olfactory and trigeminal nerves [46]. In experiments by Chao et al. (2012) on rats with unilateral lesions of the medial forebrain bundle with severe depletion (97%) of dopamine in the striatum, the hypothesis that L-DOPA can bypass the blood-brain barrier when administered intranasally was confirmed [47].

An effective method for intranasal administration of L-Dopa is the use of polymer nanoparticles. An experiment was conducted demonstrating the effectiveness of intranasal administration of L-DOPA nanoparticles with poly-lactide-co-glycolide acid (PLGA) in mice with a PD model induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [48].

An alternative method is the use of lipid-based nanoparticles. The most studied are nanoparticles based on stearic acid and lecithin (SLN). A study by Pardeshi et al. showed greater efficacy of intranasal administration of the dopamine mimetic ropiniole hydrochloride (ROPI HCl) using surface-modified polymer-lipid nanoparticles (PLN) in a PD model in mice compared to oral administration [49].

Thus, intranasal administration of levodopa results in dopaminergic modulation by bypassing the blood-brain barrier and is the most effective drug for the treatment of Parkinson's disease.

Proteins and peptides.

Proteins and peptides intranasal administration and neurodegenerative diseases:

Aberrant protein-protein interactions (PPIs) are involved in the development of such CNS diseases as Alzheimer's disease and Parkinson's disease. In this regard, there is potential for the development of peptide-based drugs that can affect PPIs [50]. Intranasal administration can be a method for overcoming the poor bioavailability of peptides when taken orally [51,52]. Proteins and peptides when administered intranasally can enter the brain indirectly, being absorbed first into the systemic bloodstream, with a further obstacle in the form of the blood-brain barrier. A more effective direct route is through the olfactory and trigeminal nerves via extraneuronal, intraneuronal, and transneuronal mechanisms [53,54]. During intraneuronal transport, peptides can be subject to degradation, so they most likely pass through the intercellular clefts of the olfactory epithelium and reach the brain by simple diffusion either through the interstitial fluid of the brain parenchyma or through the cerebrospinal fluid [55]. Cyclodextrins are used for targeted delivery of peptides to specific areas of the brain [56]. For example, alpha-cyclodextrin (6 glucose residues) increases uptake by the olfactory bulb and decreases uptake by the occipital cortex and striatum, and be-ta-cyclodextrin (7 glucose residues) increases uptake by all areas of the brain except the striatum and olfactory bulb [57]. There is evidence of neuroprotective properties of erythropoietin [58]. The administration of intranasal erythropoietin ("Neuro-EPO") to mice with an Alzheimer's disease model obtained by injection of amyloid Aβ25-35 was studied. Intranasal administration of erythropoietin reduced memory impairment, learning, and motor function in behavioral tests; in brain studies, it prevented lipid peroxidation induction in the hippocampus and reduced production of proinflammatory cytokines (TNFα, IL-1β) and Bax protein [59]. In another study, intranasal administration of erythropoietin reduced memory impairment, oxidative stress, neuroinflammation, apoptosis induction, and amyloid burden in 14-month-old APPSwe transgenic mice modeling AD [60]. Dynamine is a microtubule (MT) -binding protein that plays a key role in vesicle endocytosis. The peptide PHDP5 inhibits dynamin-MT interaction and restores endocytosis and synaptic transmission impaired by tau protein in Alzheimer's disease. A study in a mouse model of AD showed that intranasal administration of modified PHDP5 together with a cell-penetrating peptide (CPP) and the fluorescent marker FITC resulted in a significant improvement in learning and memory in the Morris water maze test compared to the control group, with results close to those in wild-type mice [61]. Nerve growth factor (NGF) is a neurotrophic protein, with the highest levels of NGF expression found in the cerebral cortex, hippocampus, and pituitary gland. NGF can in-fluence attention, arousal, motivation, memory, autonomic responses, and stress responses [62]. A preclinical study of intranasal administration of 2.5 μg NGF in mice subjected to unpredictable chronic mild stress (UCMS) demonstrated a significant decrease in immobility time in the forced swim and tail suspension tests, indicating a reduction in depressive-like behavior. In a study on rats and a dosage of 10 μg IN-NGF, an improvement in locomotor activity and an increase in the level of dopamine, norepinephrine, and expression of serotonergic receptors in the frontal cortex and hippocampus were also noted [63]. Glial-derived neurotrophic factor (GDNF) affects the development of the nervous system in the embryonic period, promotes the differentiation of midbrain dopaminergic neurons, and protects them from toxic damage, but does not penetrate the blood-brain barrier [64]. A study was conducted on the intranasal administration of GDNF to rats before a unilateral injection of 6-hydroxydopamine, which models neuronal damage in Parkinson's disease. A neuroprotective effect of GDNF was noted, with immunohistochemical studies showing the preservation of a greater number of dopaminergic neurons compared to the control group [65]. In studies on MPTP mouse models of PD, intranasal administration of GDNF encapsulated in chitosan (CS)-coated nanostructured lipid carriers with a surface modified with a transcription transactivator peptide (CS-NLC-TAT-GDNF) was used. The effect of CS-NLC-TAT-GDNF was expressed in the restoration of motor function in the rotarod test, an increase of tyrosine hydroxylase positive (TH+) neurons in the striatum and substantia nigra of the midbrain [66,67].

NAP is an 8-amino acid peptide (Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln) with some evidence of neuroprotective properties. A study of daily chronic (5 months) intranasal administration of NAP demonstrated decreased anxiety in mice in the elevated plus maze (EPM) [68]. An earlier study in rats showed improved short-term memory in middle-aged rats when tested in the Morris water maze following inhalation of NAP [69]. Exendin is a homolog of glucagon-like peptide 1 (GLP-1) and acts as an agonist of GLP-1 receptors. GLP-1 receptors are present in the hippocampus and are associated with signaling pathways involved in learning and memory, including the PI3K and adenylate cyclase pathways [69,70]. Exendin-4 improves synaptic plasticity, reduces β-amyloid levels, and protects synapses from β-amyloid toxicity [53,71-73]. Due to this, exendin can be used to treat neurodegenerative diseases such as Alzheimer's disease. Intranasal administration of exendin is four times more effective than intravenous [73]. In a study by Wang et al., intranasal exendin-4 reduced circadian rhythm disruption, memory impairment, and motor activity impairment induced by hippocampal injection of Aβ31-35 in mice [74].

Modulation of the dopaminergic and serotonergic systems via oxytocin intranasal administration:

Oxytocin, a nine-amino acid neuropeptide, plays an important role in social behavior [31]. Intranasal administration of oxytocin in a study of heterosexual couples promoted positive versus negative communication behavior during conflict discussion and significantly reduced salivary cortisol levels after the conflict [75]. Oxytocin administered intranasally can alleviate cognitive impairment in a mouse model of schizophrenia induced by dizocilpine (MK801). In the study by Ding et al. 2024, oxytocin at a dose of 6 μg/kg alleviated MK801-induced hyperactivity, sociability impairment, and spatial memory impairment, while at a dose of 20 or 60 μg/kg, it weakened hyperactivity and social novelty impairment [76]. There are studies aimed at studying the therapeutic effect of intranasal oxytocin in patients with schizophrenia. The study by Jarskog et al. involved a group of 68 people with schizophrenia and schizoaffective disorder.

Intranasal administration of oxytocin twice daily at 24 IU for 12 weeks demonstrated a reduction in negative symptoms on the PANSS scale compared to placebo in patients with schizophrenia, but not with schizoaffective disorder. However, the authors recommend caution in interpreting this association due to the many influencing factors in the study. Intranasal administration of oxytocin did not affect the social-cognitive function of patients [77]. Using the results of this study, İmamoğlu et al. concluded that intranasal administration of oxytocin does not have a significant effect on the cognitive functions of people with schizophrenia [78]. Previous studies have shown that oxytocin, administered intranasally for 3 weeks at a dose of 40 IU 2 times a day, reduced the number of points on the scale of positive and negative symptoms of schizophrenia, but the study was characterized by a small sample of patients [79].

Oxytocin is a modulator of the dopaminergic and serotonergic systems [80]. Intranasal administration of oxytocin has been shown to increase partner attractiveness compared to other men in women in relationships; this effect of oxytocin is not observed when using hormonal contraceptives [81]. In another study, intranasal oxytocin helped reduce the interest of men in relationships in photographs of unfamiliar women [82]. Intranasal oxytocin has been shown to reduce ratings of jealousy and arousal about imagined emotional and sexual infidelity of a partner of both sexes [83]. Zheng et al. suggest the possibility of using intranasal oxytocin as a safe therapeutic agent for pathological jealousy [84].

Modulation of the biological effects via growth and neurotrophic factors intranasal administration:

Huntington's disease (HD) is a genetic disorder with an autosomal dominant inheritance pattern, characterized by an increase in the number of CAG repeats in the gene encoding the huntingtin protein. There is evidence demonstrating a protective effect of insulin-like growth factor-1 (IGF-1) on neurons of the striatum [85]. A study was conducted on intranasal administration of recombinant human IGF-1 for two weeks in YAC128 mice, a model of Huntington's disease. In the control group of mice, an increase in the level of IGF-1 in the cerebral cortex, but not in the plasma, was noted. In the rotarod and open field tests, a decrease in motor impairment and an improvement in motor activity were noted. In the brain of mice after a course of intranasal IGF-1 administration, an increase in the level of AKT kinase was detected [86]. A promising direction in the treatment of Parkinson's disease is the development and use of non-toxic neuroprotectors that prevent the degeneration of dopaminergic neurons. One of the potential candidates for the role of such a neuroprotector is the HLDF-6 (Thr-Gly-Glu-Asn-His-Arg) peptide [87]. The HLDF-6 peptide exhibits broad pharmacological activity against the NMDA, glutamate, serotonin, and opioid systems, exerting a neuroprotective effect [88]. When asparagine is replaced by homoserine, the derivative peptide HDLF-6-H is formed, which is more resistant to hydrolysis. A study was conducted on mice with a model of Parkinson's disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). It was shown that long-term intranasal administration of HLDF-6 and HDLF-6-H peptides (3 weeks, 300 μg/kg/day) restored normal dopamine levels and increased its metabolic rate in the striatum [87].

In a study on a mouse model of Parkinson's disease induced by 6-hydroxydopamine, intranasal administration of insulin-like growth factor-2 (IGF-2) demonstrated a neuroprotective effect, manifested in the restoration of the level of tyrosine hydroxylase, a marker of dopamine neurons, and a decrease in α-synuclein aggregation. In vitro experiments showed that insulin-like growth factor-2 activated the phosphatidylinositol 3 kinase (PI3K)/AKT pathway [89].

The GRP78 (HSPA5) protein can modulate the unfolded protein response (UPR) and block apoptosis of dopaminergic neurons in the substantia nigra. A study was conducted showing that intranasal administration of GRP78 has a positive effect on a rat model of lactacystin-induced Parkinson's disease. Administration of exogenous GRP78 prevented the abnormal accumulation of phosphorylated pS129-α-synuclein and activation of the pro-apoptotic GRP78/PERK/eIF2α/CHOP/caspase-3,9 signaling pathway and also led to a decrease in the production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleu-kin-6 (IL-6) [90].

Kisspeptins (KPs) are a family of neuropeptides encoded by the Kiss-1 gene that exert their physiological effects through interaction with the GPR54 receptor. In one of the stages of the study by Sinen et al. 2024, the effect of intranasal kisspeptin-54 was studied in Sprague Dawley rats with stereotaxic injection of 6-OHDA into the right medial medulla to induce hemiparkinsonism. In the experimental animals, a decrease in motor deficit and a decrease in the loss of dopaminergic neurons of the nigrostriatal system induced by 6-OHDA were noted, which suggests the potential effectiveness of central administration of KP-54 in motor disorders in hemiparkinsonism.

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In another study investigating intranasal exposure to synthetic neuropeptides, in a rat model of Parkinson's disease, intranasal administration of DNSP-11 for three weeks demonstrated a significant increase in dopamine (DA) turnover in both the striatum and substantia nigra [92].

Major depressive disorder (MDD) is a common disease in the population, accounting for 4.4% of the global incidence [93]. In a postmortem study of the brain of subjects suffering from MDD, it was found that such patients are characterized by the formation of heterodimers of dopamine receptors D1-D2 in the striatum by the mechanism of direct protein-protein interaction. An interfering peptide D1-D2, consisting of 15 amino acids, capable of destroying the pathological receptor complex, was developed. When administered to rats, the peptide significantly reduced the time of immobility in the forced swim test (FST)

and decreased the number of unsuccessful escape attempts in the learned helplessness test (LH) [94]. A non-invasive intranasal administration of the interfering peptide was used in the study by Brown et al., 2014. It has been established that at doses ≥1.67 nmol/g, the interfering peptide D1–D2 has a significant antidepressant-like effect, comparable to the effect of the tricyclic antidepressant imipramine in the forced swim test (FST), lasting for 2 hours after intranasal administration [95].

The possibility of using brain-derived neurotrophic factor (BDNF) in the treatment of MDD is being studied. In the study by Ma et al., a system for intranasal delivery of BDNF together with peptides HA2 and TAT, which improve penetration through the cell membrane, was created using an adenovirus-associated virus (BDNF-HA2TAT/AAV). In behavioral experiments on mice, intranasal administration of BDNF-HA2TAT/AAV demonstrated an antidepressant effect in the forced swim test (FST) and tail suspension test (TST), as well as a decrease in depressive-like behavior in the chronic mild stress (CMS) model. The effect increased with increasing duration of drug administration. No differences in motor activity were observed in the open field test (OFT). Western blot analysis showed a significant increase in BDNF expression in the hippocampus of mice treated with BDNF-HA2TAT/AAV intranasally [96]. Later, in a rat model of post-stroke depression (PSD), intranasal administration of BDNF-HA2TAT/AAV caused a significant de-crease in immobility time in the forced swim test compared to the placebo and control groups, as well as less body weight loss over 4 weeks. Western blot and RT-PCR demonstrated an increase in BDNF expression in the prefrontal cortex compared to the control group, where BDNF expression was reduced after modeling PSD by ligation of the right middle cerebral artery. The authors suggest that the decrease in BDNF is an important link in the pathogenesis of post-stroke depression, and restoration of BDNF levels may be an effective treatment for PSD [97].

The oligopeptide lunasin, consisting of 43 amino acid residues, shows a moderate affinity for the D1 dopamine receptor. Lunasin has been shown to have effects on the central nervous system. When administered centrally to male C57Bl/6 mice at low (0.1-10 nmol) concentrations, it exerted a pronounced neuroleptic/cataleptic effect and significantly reduced amphetamine-induced hyperlocomotion [98]. The following study by Dzirkale et al. examined the effects of lunasin when administered intranasally. Intranasal lunasin completely normalized hyperlocomotion and monoamine levels in the brain of mice treated with amphetamine and DOI, but not phencyclidine, indicating possible antipsychotic activity of lunasin [99]. Neuropeptide Y (NPY) is one of the most abundant neuropeptides in the brain, and its role in regulating stress- and anxiety-related behavior has been confirmed [100,101]. The effects of NPY are mediated by at least 5 different G protein-coupled receptors (Y1, Y2, Y4, Y5, and Y6), with Y1 activation via NPY or an exogenous ligand most consistently associated with anxiolytic effects in animals [102]. A study of the tolerability and anxiolytic efficacy of intranasal neuropeptide Y in patients with post-traumatic stress disorder involved 26 patients receiving varying doses of NPY from 1.4 mg to 9.6 mg. Single doses up to 9.6 mg were well tolerated, with a dose-dependent anxiolytic effect significantly greater than placebo as assessed by the Beck Anxiety Inventory [103].

Basic fibroblast growth factor (bFGF) is a neurotrophic factor that plays an important role in the proliferation and differentiation of nerve cells, as well as in the protection of brain cells from damage and oxidative stress, thereby having the potential for the treatment of vascular dementia, the pathogenesis of which involves ischemic cell injury [104]. Intranasal administration of bFGF allows to bypass the interfering effect of the blood-brain barrier and increase bioavailability. Modern nanodrug delivery systems can be used to improve nasal absorption and bioavailability. The study by Zhang et al. investigated the effect of intranasal administration of bFGF using nanoliposomes (bFGF-lips) on learning and cognitive impairment in a mouse model of vascular dementia (VD). To model vascular dementia in mice induced by ischemia-reperfusion, a method of bilateral ligation of the common carotid arteries followed by restoration of blood flow was used. Intranasal administration of bFGF-lips significantly improved cognitive function in the Morris water maze (MWM) and novel object recognition (NOR) tests compared to the control group and the group receiving free bFGF. Histology and immunohistochemistry methods revealed a decrease in hippocampal neuron apoptosis, an increase in the concentration of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), bFGF, Bcl-2, phosphorylated protein kinase B (PAKT), nuclear factor erythroid 2-related factor 2 (Nrf2), NAD(P)H-quinone oxidoreductase 1 (NQO1), and heme oxygenase-1 (HO-1) in the hippocampus of mice [105]. Alpha-glutamyl-tryptophan (GT) is a synthetic dipeptide with immunomodulatory effects. The effects of intranasal administration of alpha-glutamyl-tryptophan and zinc arginylglycinate (AG) chelate complex on animal behavior were studied using DAT knockout rats and TAAR1 knockout mice. The anxiolytic effect was found with the combined administration of GT and AG at a dose of 100 mg in various behavioral tests. However, in the elevated maze test (EPM), a tendency towards a higher level of anxiety was observed in TAAR1 knockout mice. A single intranasal administration of AG at a dose of 10 mg/kg body weight caused a decrease in anxiety and depressive-like behavior in behavioral tests in inbred C57Bl6 mice. Both drugs demonstrated an effect on the autonomic nervous system, causing neurogenic hyperthermia when administered intranasally in a stress-induced hyperthermia test [106]. Selenoprotein T (SELENOT) is a thioredoxin-like selenoprotein, a potent antioxidant with pronounced neuroprotective activity. Based on it, the PSELT peptide was developed, which includes the redox-active site of selenoprotein T and can protect dopaminergic neurons from oxidative stress and damage [107,108]. The effect of intranasal administration of PSELT was studied in mice with a model of ADHD and comorbid pain obtained using intraventricular injections of 6-hydroxydopamine (6-OHDA) in the neonatal period. The results showed that intranasal exposure to PSELT led to a decrease in hyperactivity in the open field test (OFT), a decrease in impulsivity in the 5-choice serial reaction time task test, and an improvement in attention, as well as an increase in the nociception threshold in the hot plate test and the von

Table 1. *Biological effects of substances of peptide and amino acid nature.*

Groups of biologically active substances		Biological effects	Mechanism of action	References
Levodopa (L-DOPA)	In powder form (microparticles)	Reduction of Parkinson's disease symptoms	Conversion to dopamine by decarboxylase in the central nervous system	36,40
	Organic nanoparticles			41,43,44,45
	Polymer nanoparticles			48
	Lipid nanoparticles			49
Proteins and peptides	Exendin	Improves synaptic plasticity, reduces β-amyloid levels, and protects synapses from β-amyloid toxicity	Glucagon-like peptide 1 (GLP-1) receptor agonist. Effects on hippocampal receptors	53,70,71,72, 73,
	Insulin	Improvement of delayed memory in Alzheimer's disease	Mechanism unknown	27,32
		Reduction of sensorimotor impairments in a rat model of acute hypoxemic-ischemic encephalopathy of the newborn	Mechanism unknown	16
		Improvement of cognitive and social skills in children with Fenlan-McDermid syndrome	Mechanism unknown	17
		Hypothalamic-pituitary-adrenal axis effects	Reduction of salivary and plasma cortisol levels	20
	IGF-1 (Insulin-like growth factor-1)	Reduction of motor impairments in a mouse model of Huntington's disease	Activation of the Akt kinase pathway	86
	IGF-2	Neuroprotective, in a mouse model of Parkinson's disease	Activation of the Akt kinase pathway Phosphatidylinositol 3 kinase (PI3K)/AKT	89
	Erythropoietin	Neuroprotective	Decreased production of proinflammatory cytokines	58,59,60
	PHDP5	Neuroprotective, improved memory and learning	Inhibition of dynamin-microtubule interaction, improved synaptic transmission	61
	NGF (nerve growth factor)	Decreased depressive-like behavior, improved locomotor activity	Increased levels of dopamine, norepinephrine, and expression of serotonergic receptors in the frontal cortex and hippocampus	63
	GDNF	Neuroprotective in Parkinson's disease	Modulation of microglial function	65,66,67
	Oxytocin	Stimulation of positive communicative behavior	Decreased cortisol levels	75
	Peptides HLDF-6, HDLF-6-H	Neuroprotective action, normalization of dopamine levels in Parkinson's disease	Modulation of the expression of the neurotrophic factor BDNF and inflammatory mediators TGFβ1, IL1β and IFNγ	87,88
	GRP78	Reduction of symptoms in a rat model of Parkinson's disease	Blocking apoptosis of neurons in the substantia nigra	90
	Kisspeptin-54	Reduction of symptoms in a rat model of Parkinson's disease	interaction with the GPR54 receptor	91
	DNSP-11	Increased dopamine (DA) turnover in the striatum and substantia nigra with chronic administration	Mechanism has not been studied	92
	Interfering peptide D1-D2	Antidepressant	Disruption of dopamine receptor heterodimers D1-D2 in the striatum	94,95
	BDNF	Antidepressant	Expressed in the prefrontal cortex, the exact mechanism of the antidepressant effect is not understood	96,97

	Lunasin	Antipsychotic, cataleptic	Modulation of the serotonergic and dopaminergic system	98,99
	Neuropeptide Y (NPY)	Anxiolytic	Effect on G-protein-coupled Y receptors	102,103
	Basic growth factor fibroblasts (bFGF)	Neuroprotective, improves cognitive function in a mouse model of vascular dementia	Reduces apoptosis of hippocampal neurons	104,105
	Alpha-glutamyl-tryptophan	Anxiolytic	Mechanism of anxiolytic effect has not yet been studied	106
	Zinc arginyl glycinate chelate complex	Anxiolytic	Mechanism has not been studied	106
	NAP	Anxiolytic, neuroprotective	Antioxidant action, interaction with microtubule tubulin	68, 69
	Selenoprotein T, PSELT	Anxiolytic, neuroprotective, Antinociceptive	Exact mechanism unknown, may act via D2 receptors	109
	PACAP	Slows the progression of neurodegenerative diseases in mouse models	Increases expression of sirtuin 3 enzyme and mitochondrial function	112,113, 114,115, 116

Frey test. The antinociceptive effect of PSELT was reduced by concomitant administration of sulpiride (a D2/D3 dopamine receptor antagonist) but not phentolamine or propranolol, indicating that PSELT may modulate pain signals via the dopaminergic system [109].

Thus, intranasal administration of the proteins and peptides reduces depressive-like behavior and has a positive effect on mental and neurodegenerative diseases and memory function.

Biological effects of other peptides.

The peptide hormone ghrelin can affect the dopaminergic system in the central nervous system, regulating appetite and motivation. Ghrelin, when administered intranasally in a course (7 days at a dose of 10 mcg in 20 mcl) after exposure to a vital stressor, reduced anxiety levels and normalized compulsive behavior in an experiment on rats. Thus, ghrelin preparations can potentially be considered as correctors of obsessive-compulsive disorders against the background of post-traumatic stress disorder [110].

In recent years, there has been growing interest in intranasal administration of pituitary adenylate cyclase-activating polypeptide (PACAP) in diseases of central and peripheral neurons [111]. In rodent models, PACAP treatment slows the progression of Alzheimer's disease by protecting neurons from β-amyloid toxicity by increasing sirtuin 3 enzyme expression and enhancing mitochondrial function [112]. PACAP prevents the decline in dopamine levels in a rat model of 6-OHDA-induced Parkinson's disease [113]. Daily intranasal administration of PACAP in R6/1 mice with Huntington's disease reduced memory deficits, restored PAC1 receptor levels, and in-creased hippocampal brain-derived neurotrophic factor (hBDNF) expression [114]. In a mouse model of Alzheimer's disease, intranasal administration of PACAP was shown to improve cognitive function and increase APP processing via the non-amyloidogenic pathway, increase the ex-pression of BDNF and Bcl-2 proteins; decrease the expression of the amyloid-β receptor-transporter (Aβ) [115]. Intranasal administration of PACAP also demonstrated positive effects in studies on a transgenic mouse model of spinal muscular atrophy (SBMA) and a mouse model of vascular dementia with bilateral common carotid artery stenosis (BCAS) [116,117].

The biological effects of intranasal administration of biologically active substances of peptide and amino acid nature and the proposed mechanisms of their action are shown in Table 1.

Conclusion.

Intranasal administration of various amino acid and peptide substances, including insulin and levodopa, has anxiolytic, antidepressant, antipsychotic, neuroprotective, and other biological effects on the monoamine systems of the brain. Currently, a large amount of data has been accumulated on the mechanisms of transport of potential drugs in the nose-to-brain projection and the assessment of their therapeutic efficacy.

Thus, the non-invasive intranasal route of delivery of drugs of protein and amino acid nature is a promising method that allows bypassing the blood-brain barrier and the liver detoxification system, through various mechanisms of direct signal transmission to the brain, which can provide more effective prevention and treatment of neurodegenerative and psychiatric diseases, including Alzheimer disease, Parkinson disease, schizophrenia, depression, anxiety, and ADHD.

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Conflicts of Interest.

The authors declare no conflicts of interest.

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