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Prospects for the Rapid Delivery of Active Pharmaceutical Ingredients to the Brain for Neuroprotective Action: Examples of Nasal Gel Formulations

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INTRODUCTION & AIM

Brain diseases, including ischemic, traumatic, and neurodegenerative lesions, are among the leading causes of disability and mortality in industrialized countries. Despite significant advances in neuroscience, the problem of effective neuroprotection remains unresolved: existing pharmacological agents often demonstrate limited clinical significance, primarily due to low bioavailability and inability to cross the blood-brain barrier (BBB).

The intranasal route of administration is considered a promising alternative to traditional routes of delivery of active pharmaceutical ingredients (APIs). It allows bypassing presystemic elimination, ensures rapid entry of active substances into the systemic bloodstream and, via the olfactory and trigeminal pathways, direct delivery to brain structures. In recent years, it has been established that many compounds administered intranasally demonstrate bioavailability comparable to or exceeding that of oral administration, and in some cases close to that of parenteral administration.

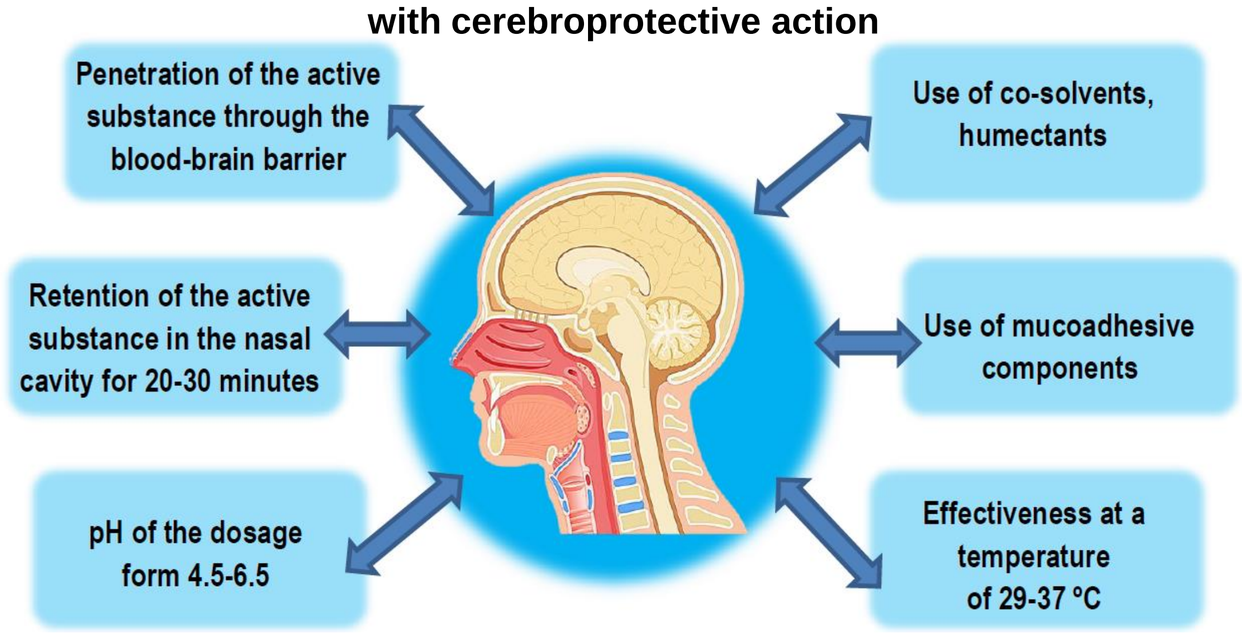
However, the rational development of intranasal forms is complicated by the need to simultaneously consider permeability through the BBB, compatibility of excipients, gel rheology, and the pharmacokinetics of nasal delivery. This requires the creation of systematic approaches that integrate information technology, *in silico* modeling, and experimental pharmacology.

The aim of this work is to develop a scientifically sound approach to the creation of intranasal gels with systemic neuroprotective action using information technology and machine learning.

METHOD

1. ***In silico* modeling.**
   Dataset of substances with characteristics of permeability through the blood-brain barrier and pharmaceutical compatibility were created. ML models of binary classification were developed to predict the penetration of active pharmaceutical ingredients through the blood-brain barrier and to assess the compatibility of components. The **ExpSys Nasalia** expert system was created to select optimal formulations.
2. **Pharmaceutical development**.
   Laboratory samples of nasal gels with three APIs have been obtained:
   - Angiolin;
   - IL-1ra;
   - Compound K.
3. **Preclinical studies**.
   A toxicological assessment and a study of local irritant and allergenic effects were conducted. Specific activity was studied in models of:
   - chronic cerebral ischemia,
   - experimental multiple sclerosis,
   - prenatal hypoxia,
   - cognitive impairment after ketamine anesthesia.

Features of the pharmaceutical development of nasal gels with cerebroprotective action



RESULTS & DISCUSSION

1. Information technology and modeling

Dataset of compounds with experimentally confirmed or presumed ability to penetrate the BBB, as well as data on pharmaceutical incompatibility of excipients, have been compiled.ML models of binary classification have been developed to predict:

(a) the ability of APIs to penetrate the BBB;
(b) the risk of pharmaceutical incompatibilities in the gel composition.

An expert information system, ExpSys Nasalia, has been created to provide automated selection of the composition of intranasal dosage forms and optimization of formulation parameters. The use of ML approaches has reduced labor costs and API consumption during the development stage by using computer prediction instead of complete experimental screening of compositions.

2. Creation of intranasal gels

Laboratory samples of gel forms of three neuroprotectors were developed:

- Angiolin — a modulator of HSP70 and glutathione systems, an activator of endogenous neuroprotection mechanisms.
- IL-1ra — an antagonist of IL-1β receptors, a biotechnological protein (17.9 kDa) that blocks pro-inflammatory cytokine cascades.
- Compound K — a triazoloquinazoline derivative, presumably interacting with GABA-A and AMPA receptors.

The gels had optimal rheological parameters, ensuring retention in the nasal cavity and stable release of the active substance.

3. Safety assessment

All three gels demonstrated no toxicity when administered intranasally once at the maximum permissible volume. No local irritation or allergic reactions were observed. The data correspond to the safety profile of the starting substances.

Specific neuroprotective activity of nasal gels

Angiolin gel	• reduced postnatal mortality after prenatal hypoxia; • decreased neurological deficits and neuronal death; • improved cognitive function, emotional status, and exploratory activity.
IL-1ra gel	• improved thiol-disulfide system parameters and reduced nitrotyrosine levels; • increased HSP70 expression; • surpassed citicoline in terms of neuroprotection; • exhibited normotimic, antidepressant, and anxiolytic effects; • reduced the number of working memory errors and the level of neuroapoptosis in a model of multiple sclerosis.
Compound K gel	• reduced anxiety and maladaptive hyperactivity after ketamine anesthesia; • improved working and reference memory performance, surpassing piracetam; • had antioxidant and anti-apoptotic effects, increasing bcl-2 levels.

CONCLUSION

This study demonstrates a successful framework for developing intranasal neuroprotective drugs using information technologies and machine learning. The three novel gels exhibited favorable safety profiles and significant neuroprotective potential in preclinical models, supporting their further development as novel therapeutic options for brain disorders.

FUTURE WORK / REFERENCES

1. Belenichev I.F., Burlaka B.S., Bukhtiyarova N.V., Aliyeva E.G., Suprun E.V., Ishchenko A.M., Simbirtsev A.S. Pharmacological correction of thiol-disulphide imbalance in the rat brain by intranasal form of Il-1b antagonist in a model of chronic cerebral ischemia// Neurochemical Journal, 2021. - №1 (15). - P. 30-36. https://doi.org/10.1134/S1819712421010153
2. Belenichev I, Aliyeva O., Burlaka B., Burlaka K., Kuchkovskyi O., Savchenko D., Oksenych V., Kamyshnyi O. Development and Optimization of Nasal Composition of a Neuroprotective Agent for Use in Neonatology after Prenatal Hypoxia. Pharmaceuticals. 2024; 17(8):990. https://doi.org/10.3390/ph17080990