

## Accepted Manuscript

Brain delivery of insulin boosted by intranasal coadministration with cell-penetrating peptides

Noriyasu Kamei, Mariko Takeda-Morishita

PII: S0168-3659(14)00741-X  
DOI: doi: [10.1016/j.jconrel.2014.11.004](https://doi.org/10.1016/j.jconrel.2014.11.004)  
Reference: COREL 7435

To appear in: *Journal of Controlled Release*

Received date: 24 July 2014  
Accepted date: 4 November 2014



Please cite this article as: Noriyasu Kamei, Mariko Takeda-Morishita, Brain delivery of insulin boosted by intranasal coadministration with cell-penetrating peptides, *Journal of Controlled Release* (2014), doi: [10.1016/j.jconrel.2014.11.004](https://doi.org/10.1016/j.jconrel.2014.11.004)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

# Brain delivery of insulin boosted by intranasal coadministration with cell-penetrating peptides

Authors:

Noriyasu Kamei, Mariko Takeda-Morishita \*

Affiliations:

Laboratory of Drug Delivery Systems, Faculty of Pharmaceutical Sciences, Kobe Gakuin University, 1-1-3 Minatojima, Chuo-ku, Kobe, Hyogo 650-8586, Japan

\*Corresponding author:

Tel: +81-78-974-4816

Fax: +81-78-974-4820

E-mail address: mmtakeda@pharm.kobegakuin.ac.jp

## ABSTRACT

Intranasal administration is considered as an alternative route to enable effective drug delivery to the central nervous system (CNS) by bypassing the blood–brain barrier. Several reports have proved that macromolecules can be transferred directly from the nasal cavity to the brain. However, strategies to enhance the delivery of macromolecules from the nasal cavity to CNS are needed because of their low delivery efficiencies via this route in general. We hypothesized that the delivery of biopharmaceuticals to the brain parenchyma can be facilitated by increasing the uptake of drugs by the nasal epithelium including supporting and neuronal cells to maximize the potentiality of the intranasal pathway. To test this hypothesis, the CNS-related model peptide insulin was intranasally coadministered with the cell-penetrating peptide (CPP) penetratin to mice. As a result, insulin coadministered with L- or D-penetratin reached the distal regions of the brain from the nasal cavity, including the cerebral cortex, cerebellum, and brain stem. In particular, D-penetratin could intranasally deliver insulin to the brain with a reduced risk of systemic insulin exposure. Thus, the results obtained in this study suggested that CPPs are potential tools for the brain delivery of peptide- and protein-based pharmaceuticals via intranasal administration.

## Keywords:

Brain delivery; intranasal route; insulin; cell-penetrating peptide; penetratin

## 1. Introduction

Recent advances in the morphology and pathophysiology of the brain have allowed the elucidation of the molecular mechanisms underlying central nervous system (CNS) diseases or disorders such as Alzheimer's disease (AD). Despite the current development of many endogenous protein- and antibody-based biopharmaceutical agents for treating CNS diseases, their therapeutic effectiveness remains inadequate [1]. One of the major obstacles is the presence of the blood–brain barrier (BBB) that mainly consists of brain capillary endothelial cells [2-4]. Because BBB strictly hampers drug influx into the brain via lipid membranes [2-4], tight junctions [5,6], and efflux systems such as P-glycoprotein and multidrug resistance proteins (MRPs) [7], only limited nutrients that can be mediated by transporters or receptors are effectively permeable across BBB [1,8,9]. Thus, many drugs, especially biopharmaceuticals, are poorly delivered to the brain. Therefore, the development of delivery systems that overcome BBB is essential for CNS pharmacotherapy.

Download English Version:

<https://daneshyari.com/en/article/7863966>

Download Persian Version:

<https://daneshyari.com/article/7863966>

[Daneshyari.com](https://daneshyari.com)