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Olfactory Transfer of Analgesic Drugs After Nasal Administration

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Abstract
Espefält Westin, U. 2007. Olfactory Transfer of Analgesic Drugs After Nasal Administration. Acta Universitatis Upsaliensis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy* 55. 64 pp. Uppsala. ISBN 978-91-554-6871-2.

Nasal administration of analgesics for achieving rapid pain relief is currently a topic of great interest. The blood-brain barrier (BBB) restricts access to the central nervous system (CNS) for several central-acting drugs, such as morphine and dihydroergotamine, which results in a substantial effect delay. Evidence for the olfactory transfer of drugs from the nasal cavity to the CNS after nasal administration, bypassing the BBB, is available for both animals and humans. The aims of this thesis were to study the olfactory transfer of morphine to the CNS after nasal administration, and to compare the nasal transport of analgesic drugs across nasal respiratory and olfactory mucosa.

In vivo studies in rodents demonstrated that morphine is transferred via olfactory pathways to the olfactory bulbs and the longitudinal fissure of the brain after nasal administration. Further, olfactory transfer of morphine significantly contributed to the early high morphine brain hemisphere concentrations seen after nasal administration to rats. Olfactory transfer was tracked by collecting and analysing brain tissue and blood samples after right-sided nasal administration and comparing the results to the situation after i.v. administration. The olfactory transfer was also visualised by brain autoradiography.

In vitro studies indicated that the olfactory mucosa should not be a major barrier to the olfactory transfer of dihydroergotamine or morphine, since transport of these drugs was no more restricted across the olfactory mucosa than across the nasal respiratory mucosa. The *in vitro* studies were performed using the horizontal Ussing chamber method. This method was further developed to enable comparison of drug transport across nasal respiratory and olfactory mucosa which cannot be achieved *in vivo*.

In conclusion, these analgesic drugs showed potential for olfactory transfer, and access to the CNS by this route should be further investigated in humans, especially for the drugs with central effects that are currently under development for nasal administration.

Keywords: Nasal administration, Olfactory transfer, Olfactory pathways, Central nervous system, Blood-brain barrier, Nasal respiratory mucosa, Olfactory mucosa, Olfactory bulb, Horizontal Ussing chamber, Morphine, Dihydroergotamine, Rat, Mouse, Swine, Autoradiography, Viability, Powder formulations

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I rörelse

Den mätta dagen, den är aldrig störst.
Den bästa dagen är en dag av törst.

Nog finns det mål och mening i vår färd –
men det är vägen, som är mödan värd.

Det bästa målet är en nattlång rast,
där elden tänds och brödet bryts i hast.

På ställen, där man sover blott en gång,
blir sömnen trygg och drömmen full av sång.

Bryt upp, bryt upp! Den nya dagen gryr.
Oändligt är vårt stora äventyr.

Karin Boye

Till Anders och Alfred

Papers discussed

This thesis is based on the following papers, which will be referred to by the Roman numerals assigned below:

I. **Westin, U.**, Piras, E., Jansson, B., Bergström, U., Dahlin, M., Brittebo, E. and Björk, E.: Transfer of morphine along the olfactory pathway to the central nervous system after nasal administration to rodents. *Eur J Pharm Sci.* 2005, 24(5): 565-573

II. **Espefält Westin, U.,** Boström, E., Gråsjö, J., Hammarlund-Udenaes, M. and Erik Björk.: Direct nose-to-brain transfer of morphine after nasal administration to rats.
Pharm Res. 2006, 23(3): 565-572.

III. Fransén, N., **Espefält Westin., U**. Nyström C. and Björk E.: The *in vitro* transport of dihydroergotamine across porcine nasal respiratory and olfactory mucosa and the effect of a novel powder formulation
Submitted

IV. **Espefält Westin, U.** and Björk E.: Morphine transport across porcine nasal respiratory and olfactory mucosa studied in horizontal Ussing chambers
Submitted

My contribution:
I contributed to all parts of the above papers except for the choice of statistical methods and simulations in Paper II, the preparation and characterisation of the powder formulation and the drug analysis in Paper III.

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