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Transdermal iontophoresis of dopaminergic (pro) drugs : from formulation to in vivo application

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Objective and outline of the thesis

1 Objective of the thesis

In the previous chapter the transdermal iontophoretic delivery of several dopamine agonists was reviewed. Despite the promising results further optimization of the transdermal iontophoretic delivery of dopamine agonists is required. The general objective of the presented research is the optimization of the transdermal iontophoretic delivery of dopamine agonists and its prodrugs for the symptomatic treatment of Parkinson's disease (Pd). To achieve this goal, the following specific items are considered:

1. Optimizing the transdermal iontophoretic delivery *in vitro* of a series of potent dopamine agonists, including rotigotine, 5-OH-DPAT and other potent structural analogs. In addition the mechanisms driving the iontophoretic transport are addressed.
2. Synthesis of novel dopaminergic prodrugs of 5-OH-DPAT with an extra chargeable group for transdermal iontophoretic delivery. Subsequently the chemical and enzymatic stability are examined. This part of the investigations was performed by Jeroen De Graan and will result in a dissertation at the Rijks Universiteit Groningen, Groningen, The Netherlands
3. *In vitro* iontophoresis of selected prodrugs of 5-OH-DPAT to investigate the feasibility for transdermal iontophoretic delivery
4. Pharmacokinetic-pharmacodynamic (PK-PD) studies in an animal model with the most promising candidates with a special focus on controlling the plasma concentration and the pharmacodynamic effect with transdermal iontophoresis
5. Evaluation and optimization of the kinetic models, developed by Nugroho et al. for the characterization of transdermal iontophoretic transport *in vitro* and *in vivo* [1-3]

2 Outline of the thesis

Part I-Optimizing the *in vitro* transdermal iontophoretic delivery of dopaminergic drugs

Although the potential of transdermal iontophoretic delivery of 5-OH-DPAT has already been demonstrated [3-4], a comprehensive characterization of iontophoresis of this potent dopamine agonist is necessary. Specifically, understanding of the mechanisms during iontophoresis driving 5-OH-DPAT across the skin barrier is essential to further improve the delivery *in vivo* in patients. In **CHAPTER 3** the optimization of the iontophoretic delivery of 5-OH-DPAT is approached from a mechanistic perspective. The influence of the following parameters is investigated: drug donor concentration, electro-osmotic contribution, influence of co-ions, current density and composition of the acceptor phase. In addition the feasibility of acetaminophen as a marker for the electro-osmotic flux is examined.

Rotigotine, another more lipophilic dopamine agonist from the 2-aminotetraline group (like 5-OH-DPAT), showed promising results when administered with transdermal iontophoresis [5-6]. However in these studies the solubility of the compound was the limiting factor for further increasing its delivery. Besides changing the donor formulation, the solubility and consequently the iontophoretic delivery can be improved by changing the salt form of the compound. In **CHAPTER 4** the influence of different salt forms of rotigotine (H_3PO_4 vs HCl) on the solubility and on the passive and iontophoretic transport efficiency is investigated. In addition the *in vitro* transport parameters are analyzed using compartmental modeling. The estimated parameters are combined with pharmacokinetic parameters from literature to evaluate the iontophoretic delivery *in vivo* in a series of simulations.

Next to 5-OH-DPAT and rotigotine, also other members of the 2-aminotetralins are very potent at the D_1 - and/or D_2 -receptor in the striatum and are potential candidates for transdermal iontophoresis. In **CHAPTER 5** the transdermal iontophoretic delivery of a series of novel dopamine agonists across human stratum corneum (HSC) and dermatomed human skin (DHS) is investigated. The molecules from the 2-aminotetraline group were selected based on their potency and molecular structure: 5-OH-MPAT, 5-OH-EPAT, 5,6-di-OH-MPAT and 5,6-di-OH-DPAT. In addition a potent chromanamine (8-OH-DPAC), which is structurally closely related to the above mentioned group, is added to the investigations. In these investigations the applicability of the kinetic models for the characterization of transdermal iontophoresis, developed by Nugroho et al., are also evaluated. The small structural

changes between the compounds tested allowed us to investigate the influence of the molecular structure and physicochemical properties on the iontophoretic delivery.

Part II-*In vivo* assessment of controlling the iontophoretic delivery of (S)-5-OH-DPAT

In **CHAPTER 6** the pharmacokinetics (PK) and pharmacodynamics (PD) following transdermal iontophoretic delivery of the active enantiomer of 5-OH-DPAT, (S)-5-OH-DPAT is investigated in male Wistar rats. The first aim of this study is to examine the relationship between the current density, the *in vivo* iontophoretic transport and the (S)-5-OH-DPAT plasma profile. To conduct transdermal iontophoresis studies, it is necessary to anesthetize the animals. Therefore the second aim of the present study is to examine the effect of the anesthetic mixture, together with the effect of transdermal iontophoresis, and blood sampling on the striatal dopamine release. This is important since the striatal dopamine release is the pharmacodynamic end-point chosen to monitor the pharmacological response following transdermal iontophoresis. The third aim is to address the PK-PD relationship following transdermal iontophoresis of (S)-5-OH-DPAT under non-saturated conditions. This implies the establishment of a controlled and reversible effect. The effect is monitored in the striatum with on-line microdialysis, while simultaneously blood samples are taken. In this chapter extensive analysis is performed with non-linear mixed effects modeling, using an integrated compartmental PK-PD model.

Part III-Transdermal iontophoretic delivery of ester prodrugs of 5-OH-DPAT: from synthesis to *in vivo* studies

In **CHAPTER 7** the transdermal delivery of 4 new ester prodrugs of 5-OH-DPAT is studied: glycine-, proline, valine- and β -alanine-5-OH-DPAT. Since ester prodrugs are susceptible to hydrolysis, stability assays are performed to select the optimal candidate(s) for further investigations. Furthermore the solubility of the prodrugs is investigated and compared to the parent drug 5-OH-DPAT. In a series of transport studies the iontophoretic delivery across HSC and DHS is examined. The main focus of the *in vitro* transport studies is to identify a prodrug that is efficiently transported with iontophoresis and which is hydrolyzed during transport through the skin. These results lead to the selection of the optimal prodrug for follow-up studies *in vivo*.

The pharmacokinetics and pharmacodynamic effect of the prodrug of (S)-5-OH-DPAT are examined in the newly developed animal model, described in **CHAPTER 6**. The resulting PK-PD parameters of the prodrug, obtained with compartmental modeling, are discussed and compared to the parameters of the parent drug (S)-5-OH-DPAT.

In **CHAPTER 8** a summary of all the results of the presented research is provided. Furthermore these results are discussed and put in perspective to the general applicability of transdermal iontophoresis of dopamine agonist for the treatment of Parkinson's disease. Finally future perspectives of transdermal iontophoresis of dopamine agonists are addressed from a mechanistic, mathematical and clinical point of view.

References

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