Pharmacokinetics and Multivariate Pharmacodynamics of Remoxipride as Fingerprint Marker: A Systems Pharmacology Approach

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Purpose
The application of pharmacokinetic (PK) – Pharmacodynamic (PD) modelling approaches in translational research has been shown to improve the survival rate of drugs through Phase II. Further improvement is envisioned via the integration of PKPD and Systems Pharmacology approaches. Systems Pharmacology includes the interrelationship between body processes at different time-scales and therefore increases the chance of finding early and holistic biomarkers for disease and pharmacological effects. Endocrine communication between brain and body is of interest to analyse the effects of CNS active compounds, for example, recently, a translational PKPD model was developed that describes the time-course of prolactin following multiple doses of the dopamine D2 receptor antagonist remoxipride. The aim of the current study is to combine quantitative PK–fingerprint PD modelling approaches for remoxipride, using endocrine communication between brain and body for eight hormones in plasma.

Methods
Male Wistar WU rats were administered 0, 6 or 16 mg/kg remoxipride (10 min intravenous infusion). Time-serial plasma and brain extracellular fluid (ECF) samples were collected (table I). Remoxipride PK in plasma and brainECF were determined by LC-MS analysis. Plasma PD was determined for Adrenocorticotropic hormone (ACTH), Brain-Derived Neurotrophic Factor (BDNF), Follicle Stimulating Hormone (FSH), Growth Hormone (GH), Luteinizing Hormone (LH), Oxytocin (OXT), Prolactin (PRL) and Thyroid Stimulating Hormone (TSH) using xMAP® technology.

Results
Results obtained so far show that Remoxipride PK in brainECF could be well characterised (fig. 1). Fingerprint PD of remoxipride was observed for the endocrine system demonstrated by the fact that plasma hormone concentrations either increased or decreased upon infusion of remoxipride (table II). For PRL the results confirmed the data obtained in our previous study. Further analysis of the data and mathematical modelling needs to be performed.

Conclusion
On the basis of the results so far obtained, this study already indicates that the fingerprint PD approach will lead to more insight in the system effects of remoxipride, as concentrations of all hormones were affected upon pharmacological perturbation of the dopaminergic system.