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# CHAPTER 1

**DYNAMICAL ANALYSIS OF BLOOD-BASED SYSTEMS  
BIOMARKERS OF CENTRAL NERVOUS SYSTEM DRUGS**

## Scope and intent of investigations

The body is a complex of interacting networks, and therefore the disciplines of pathology and pharmacology are shifting from a purely reductionist approach to a method that also includes an holistic approach [1–3]. Moreover, the biological processes related to these networks behave dynamically in response to drugs. The understanding of the dynamics of the biological processes improves the success rates in drug development [4,5]. In this thesis, we will focus on central nervous system (CNS) drug development as an example of a complex system that may suffer from a large series of serious pathologies. Neurological disorders and mental illnesses, hereafter named CNS diseases, are among the main contributors to the global burden of disease affecting millions of people worldwide [6–8]. Yet, CNS drug development is hampered by low success rates (<10%) and long duration of development (~12.6 years) [9,10]. Among other reasons, this can be attributed to lack of understanding of underlying pathological and pharmacological processes and the lack of validated biomarkers that represent these processes. Indeed, biochemical pathway analysis in cerebrospinal fluid (CSF) show a multitude of pathways involved in CNS diseases, with large overlap among CNS diseases [11]. *In silico* evaluation predicted that schizophrenia is characterized by a disbalance among the different neurochemical pathways throughout the brain that could partly be restored by antipsychotic drug treatment [12]. One of the questions is how we can translate these insights into methodologies that can be applied in CNS drug development, also considering the limitations of sampling from the human brain. In this thesis, we will therefore focus on two questions:

1. How can the relation between drug dose and the dynamic systems response be quantified *in vivo*?
2. How can blood-based markers that represent central drug effect be obtained?

### *Section I – General introduction*

In **Chapter 2** we first give a general introduction into the fields of pharmacokinetic/pharmacodynamic (PK/PD) modeling and pharmacometabolomics and how these approaches have been applied in CNS drug development. As an example, PK/PD modeling enabled interspecies translation of the prolactin response, which is a biomarker of dopamine D<sub>2</sub> receptor antagonist effect [13]. Another example showed how pharmacometabolomics reveals new lipid biomarkers to evaluate and understand the relation between D<sub>2</sub> antagonist treatment and weight gain [14]. The chapter subsequently discusses the challenges of integrating PK/PD modeling and pharmacometabolomics to enable the dynamic evaluation of the systems response upon drug treatment. A specific attention is paid to interspecies scaling in translational drug development.

**Chapter 3** describes an overview of biochemical and endocrine markers in the brain and in plasma that have been associated with dopaminergic agents. Dopamine drugs are, for

example, used to treat schizophrenia ( $D_2$  antagonists) or Parkinson's disease ( $D_2$  agonists). In addition to their interference with the dopamine pathway they also influence other neurochemical pathways [15]. Furthermore, since the  $D_2$  system is involved in the control of hormone release of the pituitary, peripheral hormone concentrations are expected to change upon administration of dopaminergic agents [16–18]. Finally, the  $D_2$  system is not only functional in the brain, in fact, it is widely distributed throughout the body being expressed in, for example, the gut, the adrenal glands and the kidney [19]. The aim of this chapter is to obtain an overview of the different biochemical and endocrine pathways in the brain and in plasma that are perturbed by these agents, to subsequently point directions to further improve biomarker-driven CNS drug development. Special attention will be paid to potential blood-based biomarkers that reflect drug effects in the brain.

### *Section II – The dynamical neuroendocrine systems response to study dopamine $D_2$ drug effects*

The neuroendocrine system provides a tight connection between the brain and the periphery. Its biological function is to control peripheral processes from the brain, such as stress and reproductive function. One of these neuronal pathways is the dopaminergic tuberoinfundibular pathway. It is well-known that activation of this pathway leads to enhanced release of dopamine into the pituitary, where it inhibits the prolactin release from the lactotrophs [17]. With regard to CNS drug development, this connection has received much attention for the discovery of blood-based biomarkers that reflect central drug effect [16].

In **Chapter 4** we use the selective dopamine  $D_2$  antagonist remoxipride as a paradigm compound to evaluate the effect of  $D_2$  antagonism on the release of pituitary hormones and neuropeptides. While prolactin has been widely used to dynamically evaluate  $D_2$  antagonistic drug effects [13,16,20], the other pituitary hormones and neuropeptides are not so often used for such evaluation. Given the biological relation between dopamine and multiple hormones, the aim of this chapter is to dynamically evaluate the neuroendocrine systems response upon remoxipride treatment in rats.

To place the results of remoxipride into perspective, in **Chapter 5**, the neuroendocrine systems response is evaluated with the selective  $D_2$  agonist quinpirole as paradigm compound.  $D_2$  agonists may be expected to interact with the neuroendocrine system inversely to  $D_2$  antagonists, but this is not necessarily the case (**Chapter 3**). Comparing agonistic with antagonistic interactions is envisioned to provide more insight into the dopamine specific effects. While single administration dynamics provide insight into the short-term mechanistic interaction between the drug and the biological system, it does not take into account longer-term processes, such as tolerance and sensitization. As these processes

involve behavioral changes upon quinpirole treatment in rats [21], the neuroendocrine systems dynamics are evaluated with single and multiple quinpirole administration.

### *Section III – The dynamical biochemical systems response to study dopamine $D_2$ drug effects*

The neuroendocrine system only represents a small part of the system-wide dopaminergic effects. Moreover, it utilizes one of the mechanisms through which blood-based biomarkers of neurological effects can be obtained. Indeed, neurochemical markers may also distribute from the brain into plasma to be discovered as blood-based biomarker. Pharmacometabolomics has proven useful for discovery of systems biomarkers of CNS drug effects and diseases [22,23]. For example, schizophrenia involves disturbances multiple metabolic pathways, including energy metabolism, neurotransmitter metabolism, fatty acid biosynthesis, and phospholipid metabolism, that are partially restored following risperidone treatment. Biomarkers such as myo-inositol, uric acid, and tryptophan were found important to distinguish disease and treatment groups [24]. Thus, pharmacometabolomics provides a powerful approach for CNS drug biomarker discovery. At the same time, there is no methodology available that quantifies the dynamical pharmacometabolomics response upon drug treatment. A logical step is the integration of PK/PD modeling and pharmacometabolomics, as is discussed in **Chapter 2**.

In **Chapter 6** a methodology is developed to describe the pharmacometabolomics data by a PK/PD model, in order to reveal the systems-wide pharmacodynamics of remoxipride in plasma. The aim of this chapter is to quantify the multiple dose-response relationships underlying the systems-wide effects of remoxipride in terms of pharmacologically meaningful parameters such as potency ( $EC_{50}$ ), maximal effect ( $E_{MAX}$ ) and endogenous metabolite turnover rate ( $k_{OUT}$ ). Here, it is important to describe the pharmacokinetics of remoxipride simultaneously with the pharmacodynamics, in order to account for potential temporal delays between drug concentration and biomarker profile. Additionally, biomarkers that represent the diverse response patterns are presented for future validation.

The PK/PD-metabolomics method is taken a step further in **Chapter 7** in which we describe multiple biomarker responses in plasma as well as in brain extracellular fluid upon administration with quinpirole. Again, it is important to describe the pharmacokinetics and the pharmacodynamics simultaneously, but now with an additional layer of complexity: biomarker responses in brain as well as in plasma. This provides us the opportunity to identify response patterns that are specific for the brain or the periphery. Moreover, for biomarkers that show a response in brain as well as in plasma, we can indicate the target site of action by comparing the temporal response patterns in both biofluids. We show that multiple biomarkers respond in the brain and in plasma with different pharmacodynamic

characteristics (e.g.  $EC_{50}$ ,  $E_{MAX}$ ,  $k_{OUT}$ ). We also present potential (blood-based) biomarkers of quinpirole effects for future validation.

#### *Section IV – General discussion and conclusion*

In **Chapter 8** we give an overall reflection on the results in the different chapters, discuss the implications of our findings, and provide directions for future research on the integration of PK/PD modeling and pharmacometabolomics in CNS drug development.

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