Multi-biomarker pharmacokinetic-pharmacodynamic relationships of central nervous systems active dopaminergic drugs

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CHAPTER 2

BUNDLING ARROWS: IMPROVING TRANSLATIONAL CNS DRUG DEVELOPMENT BY INTEGRATED PK/PD-METABOLOMICS

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Abstract

Introduction: Central nervous system (CNS) diseases affect millions of people worldwide, and the number of people is quickly growing. Unfortunately, the success of new CNS drugs in clinical development is less than 10%, and this has been contributed to the complexity of the CNS, unexpected side effects, difficulties for drugs to penetrate the brain and the lack of biomarkers.

Areas covered: First, we discuss how pharmacokinetic/pharmacodynamic (PK/PD) models are designed to predict the dose-dependent time course of effect, and how they are used to translate drug effects from animal to men. Then, we discuss how pharmacometabolomics provides insight into system-wide pharmacological effects and why it is a promising method to study interspecies differences. Third, we advocate the application of PK/PD-metabolomics modeling to advance translational CNS drug development by discussing its opportunities and challenges.

Expert opinion: It is envisioned that PK/PD-metabolomics will increase understanding of CNS drug effects and improves translational CNS drug development to increase success rates. Successful further development of this concept will need multi-level and longitudinal biomarker evaluation over a large dose range, multi-tissue biomarker evaluation, and the generation of a proof of principle by application to multiple CNS drugs in multiple species.

Key words: Biomarkers; CNS drug development; Interspecies scaling; Pharmacometabolomics; PK/PD modeling; Systems pharmacology

Highlights

1. Translational CNS drug development is shifting from an empirical to a mechanistic approach
2. PK/PD modeling in conjunction with scaling principles enables the interspecies translation of pharmacological CNS effects
3. Pharmacometabolomics provides a mean to compare the system-wide pharmacological CNS effects in multiple species
4. An integrated PK/PD-metabolomics is envisioned to increase understanding of CNS drug effects and improve translational CNS drug development
5. To achieve an integrated PK/PD-metabolomics approach, we need multi-level biomarker evaluations, to study a large dose range, and longitudinal sampling from the brain, plasma, and CSF.

1. Introduction

Central nervous system (CNS) diseases affect millions of people worldwide, and the number of people with such disease is quickly growing [1]. They are characterized by their high complexity as multiple neurotransmitter systems and biochemical pathways are involved [2–4]. It is therefore not surprising that CNS drug development suffers from low success rates (< 10%) and long duration (~12.6 years) [5,6]. Moreover, it is hampered by CNS mediated side effects (e.g. nausea, dizziness), the presence of the BBB, lack of effective animal models and/or lack of integrative investigations in animals to investigate the mechanisms of CNS pathology and pharmacology, and the lack of biomarkers representing these mechanisms [6–9]. In particular, the translation from preclinical to early clinical studies is difficult.

Clearly, there is a need to improve the current methodologies within CNS drug development. Two promising methods in this regard are pharmacokinetic/pharmacodynamic (PK/PD) modeling and pharmacometabolomics [10–12]. PK/PD modeling allows to "characterize and predict the time course of drug effects under (patho)physiological conditions" [13]. Pharmacometabolomics involves the "determination of the metabolic state to define signatures before and after drug exposure that might inform treatment outcomes" [14]. This review discusses how translational CNS drug development can be improved by the integrated application of PK/PD modeling and pharmacometabolomics. An overview will be provided of the role of both fields in translational CNS drug development, after which the opportunities and challenges of an integrated approach will be discussed.

2. Biomarker-driven development of central nervous system drugs

Current translational CNS drug development highly relies on behavioral endpoints, such as the 5-choice serial reaction time task. While these endpoints may provide reasonable construct validity, their predictive validity is low [15,16]. Predictive validity, which includes a mechanistic rationale between the drug effect and the endpoint, is important to translate the preclinical to the clinical pharmacology [17]. It is therefore that biomarkers are increasingly recognized as an essential element of CNS drug development [7,18–20]. Indeed, biomarkers have been defined as indicators of specific pharmacological or physiological processes [21,22]. Current biomarker strategies include receptor occupancy [23–25], functional imaging [26,27], biochemical measures in CSF [20], EEG [28,29], or physiological measures such as hormone release [30]. Biomarkers have been classified into multiple pharmacological levels following the causal relation of the drug dose to the clinical effect [31]. These are i) genotype or phenotype, ii) drug exposure, iii) target occupancy, iv) target activation, v) physiological/laboratory measures, vi) disease processes, vii) clinical scales.

Such classification provides a framework for rational drug development. In particular, as depicted in Figure 1, confidence in the drug exposure, target binding, and target activation are key components to guarantee successful translational drug development [12].
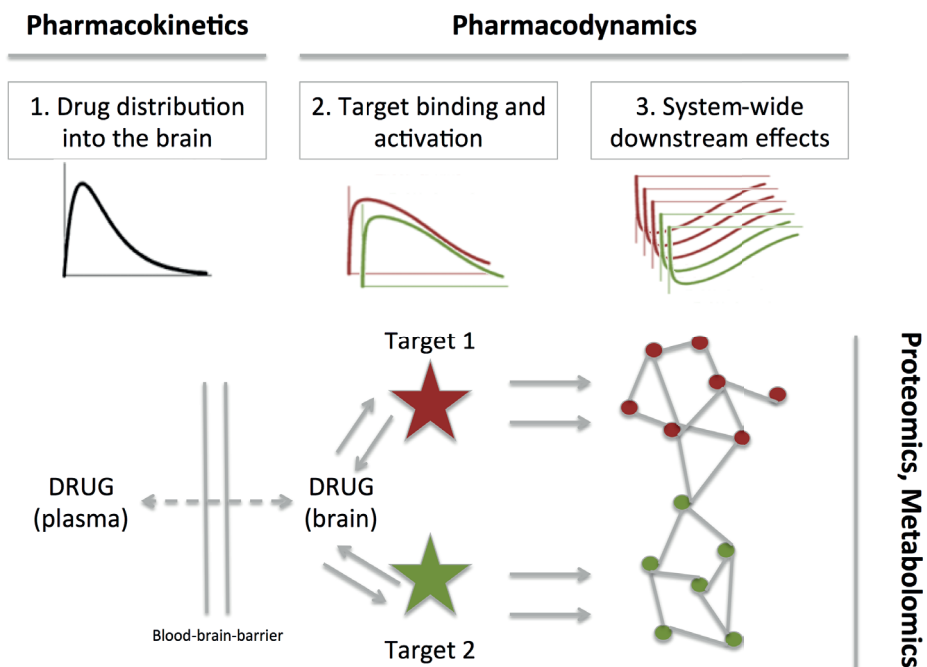

Figure 1. The conceptualization of an integrative approach. The plasma and brain drug exposure profile are determined by the pharmacokinetics, to drive the target binding and activation of potentially multiple targets. The activation (or inhibition) of these targets elicits multiple downstream biochemical effects, which can be evaluated by proteomics or metabolomics. These processes are described by mathematical expressions as developed in the field of PK/PD modeling.

3. PK/PD modeling in biomarker-driven CNS drug development

Not only the measurement of biomarkers is important for prediction of the dose-effect relation. It is also important to quantify the non-linear and time-dependent relations between the biomarkers to obtain insight into the dynamics of the pharmacological processes. PK/PD modeling is used to mathematically describe these processes in terms of PK and PD parameters, for example, clearance, volume of distribution, maximal drug effect or *in vivo* potency. Biomarkers thus enable the quantitative characterization of the processes that are on the causal path between dose and effect. More specifically, biomarker data gives insight into pharmacokinetic (PK) parameters such as clearance and volume of distri-

bution, or pharmacodynamic (PD) parameters such as maximal effect and *in vivo* potency. As such, PK/PD parameters provide a quantitative and scalable perspective on interspecies differences, thereby allowing the prediction of the first-in-human dose [17,30,32]. The components of a PK/PD model are the i) PK model that describes the exposure of the drug in the body; ii) the PD model that captures the relation between the drug concentration and the effect and iii) the link model that accounts for the possible delay between the concentration-time and the effect-time profile [13]. These components are further described in the next section.

3.1 PK/PD models

3.1.1 PK models

A crucial aspect of successful CNS drug development is the understanding of the distribution of the drug into the brain [33–35]. The intensity, onset, and duration of CNS drug effects depend on the concentration-time profile at the site of drug action. This brain is separated from the plasma by the blood-brain-barrier (BBB), which often influences the rate and extent of drug distribution into the brain. The transport over this barrier may be passive (driven by concentration gradient) and active (driven by transporters). In addition to the BBB, other factors, such as plasma protein binding, brain tissue binding, cellular uptake, brain metabolism, CSF flow, and physicochemical properties of the drug influence the drug exposure profile in the brain (for reviews and key research on this topic see references [36–41]). Although classical PK modeling still often is used, physiology-based PK (PBPK) modeling is increasingly applied to predict the time course of drug concentrations at the site of drug action.

3.1.2. PD models

Whereas the understanding of the drug exposure at the target site is a crucial aspect in CNS drug development, the subsequent linkage to the PD (i.e. target binding and activation, and downstream physiological responses) is equally important for understanding drug effects [11,12]. Among others, receptor occupancy [23,25], EEG measures [28,42], hormone release [30] have been used to characterize the pharmacodynamic response of CNS drugs. The mathematical linkage of PD responses to the drug exposure has been extensively reviewed by Danhof et al. (2007) [43]. Still, in practice, an integrative approach including PK and PD in one study is often lacking. A widely used equation to link PK to PD is the empirical sigmoid E_{max} equation:

$$E = \frac{E_{max} \cdot C}{EC_{50} + C},$$

(1)

where E_{max} is the maximal observed drug effect, EC_{50} is the *in vivo* potency and C is the concentration around the target (e.g. brain$_{ECF}$).

3.1.3 Link models

The effect-time profile is often delayed as compared to the drug concentration-time profile. If only plasma drug concentrations are known, one may assume that the delay is caused by slow distribution from plasma to the site of drug action. In such case, an effect compartment model is used to account for the delay [44]. Slow target binding kinetics may also cause a delay between PK and PD, and in such case, these can be explicitly included in the model [45]. Finally, downstream signal transduction may be relatively slow compared to the plasma PK, drug distribution, and the target binding kinetics, being responsible for the delay of the effect-time profile. This is often accounted for by a turnover model [46]. It assumes a continuous process of production and degradation (turnover) that drives the basal biomarker levels. The drug effect influences either the production or the degradation rates through inhibition or stimulation, thereby causing an increase or a decrease of the biomarkers levels.

3.2 Interspecies scaling

PK/PD modeling enables the rational extrapolation of drug effects between animal and men [47]. It does so by explicitly distinguishing the drug- and system-specific parameters [17,32]. Typical drug-specific parameters are plasma protein binding, target-binding affinity, and intrinsic efficacy, while examples of system-specific parameters are tissue volumes, clearances, receptor expression, and turnover rate constants. While drug-specific parameters can be obtained from *in vitro* experiments, system-specific parameters can only be estimated from *in vivo* data and may be species-dependent. The interspecies scaling of these parameters follows two principles: allometric scaling and physiology-based scaling. With allometric scaling it is assumed that the parameters are dependent on bodyweight following a power function [48,49]:

$$P_{hum} = P_{animal} \cdot \left(\frac{BW_{human}}{BW_{animal}} \right)^b , \qquad (2)$$

where P is the mathematical model parameter, BW is the bodyweight, and b is the species-independent scaling exponent. Typically, allometric scaling is applied to clearance, volume of distribution, and turnover rate constants. The scaling exponent generally is 0.75 for the clearance, 1 for the drug distribution volume and -0.25 for the turnover rate constant [50,51]. As an illustrative example, the acetaminophen clearance extrapolates over a large range of species, including zebrafish larvae, rat and human, using allometric scaling [52].

In another study, the prolactin effects of remoxipride were successfully scaled from rat to man, by applying allometric scaling on the turnover rate of prolactin in plasma [30].

The principle of physiology-based scaling is to replace the animal parameters by the human parameters [53]. While the physiology-based scaling of CNS PK is well developed, for example to predict the human CSF drug concentrations of acetaminophen and morphine [37,39,54,55], it has only started to emerge for PD. Some studies have shown that PD parameters such as E_{max} and EC_{50} may be similar across species for a series of drugs, for example for opioids and their effect on electrocardiogram output [29,56]. In contrast, other studies showed species-dependent PD parameters. A recent evaluation of a Transient Receptor Potential Melastatin-8 blocker showed 3-fold cross-species (mouse versus dog) differences in its potency, resulting in clinically important differences in core body temperature predictions [57]. In another study, the E_{max} and EC_{50} for prolonging the QT-interval were found to differ between humans and dogs [58]. A third publication showed that the affinity of psychoactive drugs differed significantly between, for example, the $D1_{rat}$ and $5HT2_{rat}$, and $D1_{human}$ and $5HT2_{human}$ receptors [9]. Also, the E_{max} and the EC_{50} of prolactin to control its own release was found different between rats and humans [30].

Overall, these examples show that the interspecies translation of CNS drug effects needs to be driven by the mechanistic understanding of drug- and system-specific properties at the level of PK and PD. Both allometric scaling and physiology-based scaling of PK/PD parameters can be used to support interspecies translation on basis of *in vitro* (drug-specific) and *in vivo* (system-specific) parameters. If clinical data is not available from same-in-class drugs, multiple species can be evaluated for these properties and simulations of worst-to-best case scenarios can be used to guide the dosing strategies during early clinical development [57].

4. Pharmacometabolomics in biomarker-driven CNS drug development

Although PK/PD modeling aims to predict single biomarker time courses, it appears that CNS drugs typically affect multiple biochemical pathways [59,60]. For example, risperidone affected multiple pathways including energy metabolism, antioxidant defense systems, neurotransmitter metabolism, fatty acid biosynthesis, and phospholipid metabolism [61]. In fact, many successful CNS drugs were identified by serendipity on basis of phenotypic changes *in vivo* [62]. Indeed, the efficacy of neurological drugs is associated with multi-target affinity [63–65]. As an example, antipsychotics typically have interactions with multiple targets (up to 26 for clozapine and quetiapine) [63,64]. A comparison of haloperidol and clozapine showed that they caused a different biochemical phenotype,

that of clozapine close to that of the 5-HT$_{2A}$ antagonist M100907 [66]. However, although multi-target pharmacology may be related to the efficacy of e.g. clozapine, it is also associated with unwanted effects, for example cardiovascular disease [63]. Good insight into the systems behavior of multi-target drugs is essential to anticipate the (post-)clinical benefit-risk balance of drugs during early development. As such, pharmacometabolomics is suggested as an important method in drug development to biochemically understand *in vivo* neuropharmacological effects [67–69]. For example, using lipidomics, the underlying pathways were identified that may explain antipsychotic-induced weight gain [70]. Metabolomics analyzes hundreds of biochemical molecules in biological samples, and as such, it can provide system-wide pharmacological biomarkers [14]. By measuring the biochemical end-products of cellular reactions it provides an intermediate metabolic phenotype between gene expression and drug effects on one hand, and clinical outcome on the other hand. In other words, it fulfills the definition of a type 4 biomarker [31] and can provide insights into the pharmacological pathways relevant to the clinical outcome. For example, a urinary metabolomics fingerprint could be used to predict the Kellgren-Lawrence grade as a clinical endpoint for osteoarthritis [71]. As compared to other biomarker types, such as functional imaging, pharmacometabolomics is relatively cheap and easy to apply in preclinical and early clinical studies. Moreover, biochemical pathways are relatively similar across mammalian species, suggesting potential for applying pharmacometabolomics in translational drug development [72,73]. The main analytical tools that are used for metabolomics are nuclear magnetic resonance (NMR) technology and liquid chromatography-tandem mass spectrometry (LC-MS/MS). Both technologies have the advantage that they can identify a wide range of small molecules, providing a comprehensive picture of the metabolome. The metabolome contains more than 40000 molecules, which typically have a molecular weight below 2 kD [74].

Of interest for the CNS-pharmacology are the energy substrates, neurotransmitters, amino acids and structural lipids, all of which are involved in cell viability, signaling, and cell membrane function [2]. It was specifically observed that the corresponding pathways were overlapping among CNS drugs and diseases, indicating that multi-biomarker approaches are important for the evaluation of drug effects [2,59]. Several clinical studies have been performed utilizing pharmacometabolomics for the study of CNS drug effects, although the main focus has been on the disease rather than on the treatment [75]. These studies showed that pharmacometabolomics has the potential to reveal new insights into lipid-related side effects of antipsychotics [70,61], enable the early prediction of antidepressant effects on multiple biochemical pathways [76], or identify systems biomarkers of motor neuron disease treatment [77] and antiparkinson drugs [78].

4.1 Multivariate analysis of pharmacometabolomics data

The endogenous metabolites are members of biologically highly connected pathways. Pharmacometabolomics data is therefore often evaluated by multivariate data analysis, which takes into account the connectivity among the individual metabolites. The purpose is to identify biomarkers that classify subgroups (e.g. treated vs. non-treated), and to elucidate the biochemical pathways that are perturbed with drug treatment. There are roughly three types of multivariate analyses: descriptive analyses (e.g. correlations), unsupervised methods, and supervised methods. (for review see [79]). An example of descriptive analysis is correlations between metabolite levels. These can be used to define a network with metabolites as nodes, while edges are drawn if the correlation coefficient exceeds a certain threshold (e.g. 0.8). In addition to correlation-based networks, more sophisticated methods have been developed, such as Gaussian graphical networks. These networks eliminate the direct correlations that are explained by indirect correlations, providing a much cleaner network [80,81]. The power of network analysis is that it shows a clear picture of the multifactorial changes under particular conditions, for example, treated vs. non-treated. In particular, it can identify the key metabolite pathways that underlie the pharmacological effects [82], as well as their synergistic or resilient characteristics [83]. A network approach was, for example, used to understand the systems-wide effects of sertraline, showing that the tricarboxylic acid and the urea cycle, fatty acids and intermediates of lipid biosynthesis, amino acids, sugars and gut-derived metabolites were changed with four-week treatment [76]. A well-known unsupervised method is cluster analysis, which classifies samples or metabolites on basis of the proximity to each other with regard to, for example, the metabolite levels or the chemical similarity. This can reveal interesting patterns in the data, such as clusters of genes or metabolites that have similar biological functions [84]. Another well-known unsupervised method is principal component analysis (PCA), which identifies the latent variables (principal components) underlying pharmacometabolomics data [85]. These latent variables then represent the 'overall' effect of a treatment in case of a pharmacometabolomics study. Closely related to PCA is the supervised partial least squares regression (PLS). This method optimizes a model to predict a certain output variable, for example, disease status or dose [77]. Both PCA and PLS elucidate which metabolites are most influential in explaining the variation between the subgroups.

4.2 Translational pharmacometabolomics to study CNS drug effects

The specific application of metabolomics in translational drug development has gained attention more than 10 years ago [72]. Metabolomics has an advantage over other 'omics' approaches with regard to interspecies translation. Indeed, endogenous metabolite pathways are highly identical among mammalian species. A recent study thoroughly compared the biochemical reaction network of rat and human, showing a strong overlap [73]. There

are, however, only a few studies that applied metabolomics *in vivo* to compare different species. Some studies showed how the metabolic phenotype of animal disease models for osteoarthritis and multiple sclerosis overlapped with the patients' metabolic phenotype, indicating the potential of metabolomics for interspecies translation [72,86,71,87]. Although no efforts have yet been made to compare the animal and human metabolic phenotypes after drug treatment *in vivo*, the rat and mouse metabolic phenotypes were compared to study their differential sensitivity to cocaine [88]. It was found that the aryl hydroxylation pathway was dominant in rats, causing increased excretion of cocaine, which was not the case in mice. Interestingly, when comparing microsomes of humans versus these two species, the human cocaine metabolism showed a closer resemblance to the mice cocaine metabolism, indicating that the mouse is a better animal model for evaluation of cocaine sensitivity in humans. This study shows how pharmacometabolomics could be used to guide interspecies translation of CNS drug effects. Nevertheless, care should be taken with regard to the assumption that the biochemical reaction networks are species independent. The bile acid, carbohydrate, glycine-serine-threonine, purine and ascorbic acid pathways were found to have reactions specific for rats, while the glycan and sphingolipid pathways included human specific reactions, as measured in hepatic cells. These species differences may result in large differences in even opposite effects on certain endogenous metabolites [73]. In such case, further information on the pathway is important to extrapolate the preclinical findings. The ascorbic acid change in rats, for example, reflects a change in the glucuronic acid metabolism, which is also present in humans [89]. This information can then be used for the interspecies translation.

5. The integration of pharmacometabolomics and PK/PD modeling in translational CNS drug development

Translational CNS drug development can thus potentially profit from both PK/PD modeling and pharmacometabolomics; both are envisioned to contribute to biomarker-driven development. An integration of PK/PD modeling and pharmacometabolomics is envisioned to provide scalable system-specific parameters for multiple biochemical pathways that are potentially relevant for the clinical drug effects. A conceptual workflow of such translational approach is depicted in Figure 2. Recent suggestions have been made to use pharmacometabolomics in PK/PD frameworks as static or dynamic markers [90,91]. While static metabolic phenotypes can be used as a predictor for treatment responses, dynamic metabolic phenotypes allow to follow the treatment effect over time to evaluate the system-wide dynamics [90,92,93].
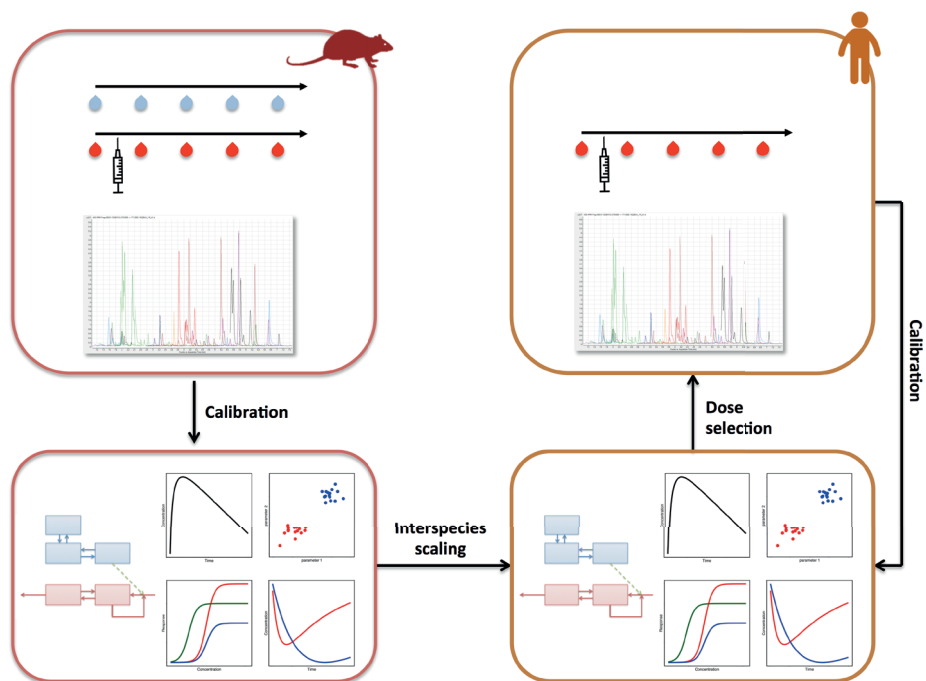
Figure 2. The integrative approach of metabolomics and PK/PD modeling as applied to interspecies scaling in CNS drug development. Such approach starts with animal experiments to collect longitudinal brain$_{ECF}$ and plasma samples during treatment with a CNS drug. These samples are analyzed for drug concentrations and metabolomics to subsequently develop a multivariate PK/PD model. By applying the principles of interspecies scaling a humanized model is defined to select doses for the clinical study. Plasma drug concentrations and metabolomics data of the clinical study will be used to recalibrate the model and increase the understanding of interspecies differences.

5.1 Longitudinal analysis of pharmacometabolomics responses

A longitudinal multivariate evaluation of pharmacometabolomics data was performed by Rasmussen and colleagues, who were one of the first doing that in the field of clinical pharmacology [94]. This multivariate fingerprint was suitable for guiding dose selection of recombinant interleukin-21 in patients with metastatic melanoma.

5.2 PK/PD based analysis of pharmacometabolomics responses

In addition to longitudinal evaluation of the pharmacometabolomics response, the integration with PK/PD modeling has been shown in a few studies. Clustering of longitudinal transcriptomics data formed the basis for the 6 turnover models in one study. Together, these turnover models formed a complex PK/PD model that described the gene-expression signaling cascade in the rat liver after corticosteroid treatment [84]. In another study, clustering was applied to the PK/PD parameters identified from pharmacometabolomics data

in rats after remoxipride treatment [95]. This analysis revealed 6 unique PK/PD relations, 18 potential biomarkers and two perturbed pathways (Figure 3). It has the potential to define a therapeutic window on basis of multiple biomarkers, provides a list of biomarkers to take into account in additional studies, and gives insight into biological effects of remoxipride. The application of such analysis in multiple species will give insights into species-differences on the PK/PD parameters that describe the longitudinal pharmaco-metabolomics response. Depending on the differences in parameters, dosing strategies can be defined following simulation of worst-to-best case scenarios as was performed by Gosset *et al.* [57] for the effect of a Transient Receptor Potential Melastatin-8 (TRPM8) blocker on a single marker (core body temperature). Eventually, pharmacometabolomics data analysis methods can aid the development of quantitative systems pharmacology (QSP) models which aim to mathematically describe the interactions between multiple elements of the biological system (e.g. biomolecules, cells, tissues) in order to understand the impact of drugs on the system as a whole [91,96,97]. Quantitative metabolic networks can provide a topological basis of QSP models to be integrated with organ-level networks, receptor binding kinetics and PK [91,97]. QSP models are promising for interspecies translation by humanizing the animal-based model parameters [9,98,99].
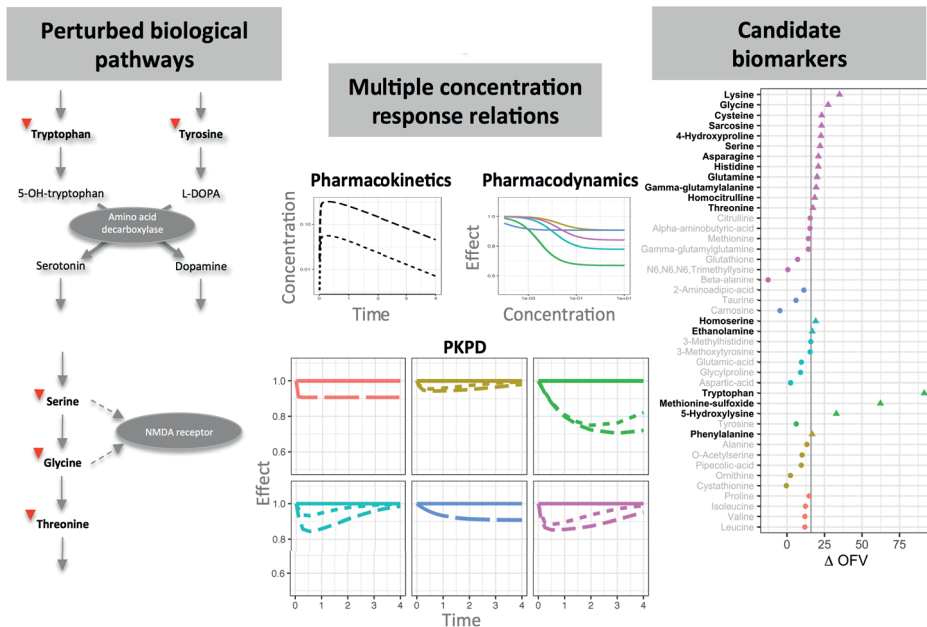

Figure 3. A metabolomics study combined with multivariate PK/PD modeling revealed 6 diverse response patterns (middle) for remoxipride in rats. These response patterns were represented by 18 metabolites that could potentially function as biomarker (right), rendering further validation. The response clusters were associated with 2 known biological pathways (left). Modified from reference 95.

5.3 Prediction of the human brain pharmacometabolomics responses

In vivo pharmacometabolomics studies typically use plasma samples to characterize the system-wide drug effects. The plasma metabolic phenotype is a composite extraction of all individual tissue metabolic phenotypes. Although this provides the opportunity to evaluate whole-body treatment effects in an easily accessible body fluid, it can limit the quantitative interpretation of the treatment response that originates in a specific tissue. This is particularly true for CNS treatments, for which the metabolic biomarkers have to distribute over the BBB (Figure 4). This was illustrated by the fact that plasma monoamine levels were decreased with CNS drug treatment, whereas CSF levels were not affected [20,78]. Likely, the effects were caused in the periphery, and did not provide information on the central brain effects of these drugs.
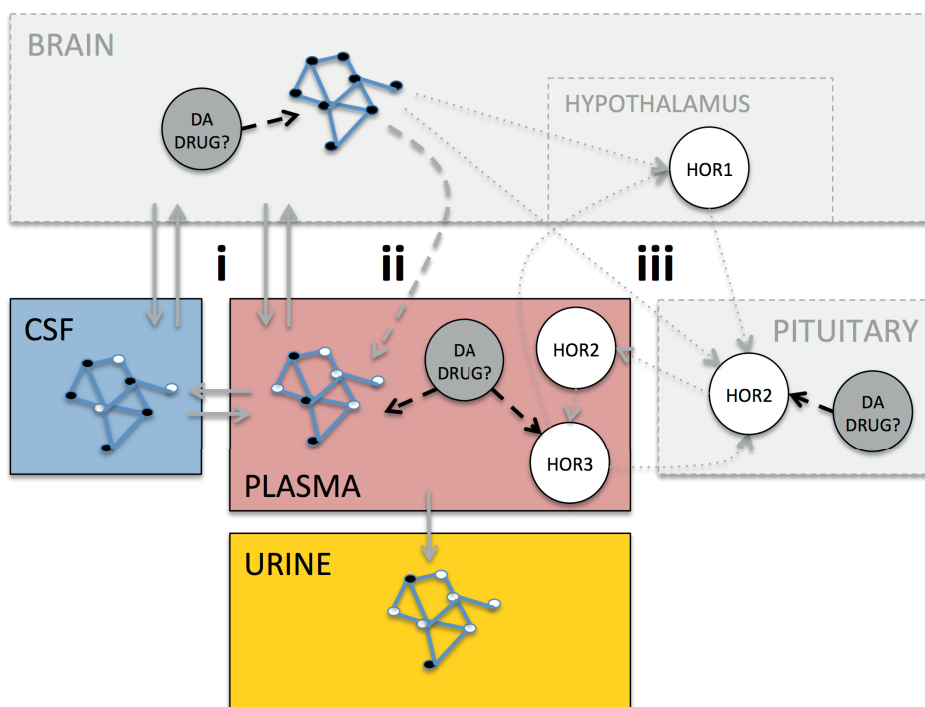

Figure 4. Brain metabolic phenotypes are reflected in the periphery via three mechanisms: i) individual metabolites distribute to CSF, plasma and urine, and become integrated in the peripheral metabolic phenotype; ii) the brain metabolic phenotype affects the peripheral nervous signaling, thereby controlling the release of peripheral metabolites, such as acetylcholine or norepinephrine; iii) the brain metabolic phenotype influences the neuroendocrine system via the hypothalamus, modifying the pituitary hormone release. Modified from reference 59.

A useful technique that has been used to study CNS drug PK and PD is intracerebral microdialysis [100–103]. It allows longitudinal sampling within a single individual to follow the treatment response over time. Moreover, since microdialysis allows the collection of molecules with a molecular weight below 20 kD, it is highly suitable for pharmacometabolomics analysis [104,105]. Notably, microdialysis, for ethical reasons, is limited in humans. Animals are therefore typically used to characterize the relation between the brain- the CSF- and the plasma metabolic phenotypes. Following the translation PK/PD-metabolomics workflow depicted in Figure 2, the human brain metabolic phenotype can subsequently be predicted using the principles of interspecies scaling and calibrated with the human plasma and CSF metabolic phenotypes.

5.4 Disease dependent PK/PD-metabolomics approach

This review has mainly focused on the treatment, rather than on the disease. Here, we would like to spend a few words on the influence of pathology on the pharmacology; a patient may respond differently to a treatment than a healthy individual. Both the CNS drug PK and PD can be affected by the disease, and this influence is drug-specific. For example, the morphine PK changed with traumatic brain injury [39], and the rate of dopamine metabolism was higher in a rotenone rat model of Parkinson's Disease as compared to control [103]. Thus, the understanding of the two-way interaction between pathology and pharmacology in the context of translational CNS drug development is important. Metabolomics was found useful to understand species differences with regard to pathology [72]. As such, it has potential to translate the pathology-dependent pharmacology from animal to men [106].

6. Conclusion

This review discussed the merits of PK/PD modeling and pharmacometabolomics in the field of translational CNS drug development. PK/PD models can predict human biomarker time courses on basis of animal data using the principles of interspecies scaling. Pharmacometabolomics can measure the biochemical responses to evaluate the system-wide CNS drug effects among species. The integration of PK/PD modeling and pharmacometabolomics studies is envisioned to enable the prediction of longitudinal, dose-dependent system-wide responses, and has begun to receive attention [90,91,95]. The opportunities and challenges of such integration were discussed with regard to translational CNS drug development. Although we are still at the stage of early conceptual development, such integration is envisioned to increase understanding of system-wide pharmacology and to improve the interspecies translation of CNS drug effects.

7. Expert opinion

7.1 The potential of integrated PK/PD and pharmacometabolomics in translational CNS drug development

CNS drug development is suffering from low success rates, which, for a large part, can be attributed to the empirical approach in translational development [6,12]. This led to the realization to shift towards mechanism-based prediction of clinical on basis of pre-clinical pharmacology. In particular, PBPK and PK/PD modeling are increasingly applied in drug development to guide dosing strategies for early clinical studies [39,47,57,107]. The strength of these models is that they describe the dynamics of pharmacological processes, which can be scaled from animals to humans. While the PD models typically describe the drug effect on a single biological pathway, pharmacometabolomics provides a means to evaluate multiple pathways obtaining a comprehensive insight into the system-wide pharmacology of a CNS drug [69,108]. Interestingly, the metabolome is structurally very similar among mammalian species, enabling a direct comparison of their metabolic phenotypes, although there are a few differences that need caution (e.g. ascorbic acid production in rats, but not in humans) [72,73]. At this moment, only very few studies have been performed to investigate the interspecies correlations of metabolic phenotypes. Moreover, pharmacometabolomics is mostly applied in a static manner, although dynamic approaches are emerging [90,94,95].

PK/PD modeling and pharmacometabolomics are thus complementary to each other. Since both fields have a potential for translational CNS drug development, their integration is promising. It has the potential to identify the pharmacologically relevant parameters of the system-wide drug effects [95]. Using the principles of interspecies scaling, these parameters can be humanized, and predict the clinical on basis of the preclinical pharmacology. The model can subsequently be validated on basis of the clinical metabolic phenotype (Figure 2).

7.2 Challenges and recommendations for the integration of PK/PD modeling and pharmacometabolomics

Several aspects of study design and data analysis need consideration to achieve an integration of PK/PD modeling and pharmacometabolomics.

7.2.1 Multi-level biomarker evaluation

To achieve an integrative understanding of the pharmacological action, multi-level biomarker data needs to be collected, for example, plasma drug concentrations, brain drug concentrations, (multiple) target occupancies, biochemical biomarkers. Eventually, these biomarkers will be linked to physiological measures and clinical outcome during clinical development.

7.2.2 Longitudinal sampling over a large dose range

To capture the dynamics of the PK/PD response, longitudinal data is essential. Serial plasma sampling and intracerebral microdialysis are useful methods to obtain time courses of CNS drug concentrations, as well as biochemical markers, in plasma and brain. Of interest, isotope-labeling based metabolomics (also called flux-based metabolomics) is an emerging discipline that enables the capturing of network dynamics when applied in combination with longitudinal sampling [109,110]. Additionally, a large drug concentration range is needed to have information on all parts of the non-linear concentration-response curve. This is particularly important with a comprehensive pharmacometabolomics evaluation, since individual metabolites may have a different position on the concentration-response curve [95].

7.2.3 Integrated PK/PD-metabolomics analysis

Longitudinal pharmacometabolomics data in conjunction with drug concentration data needs to be described using PK/PD modeling in order to identify a fingerprint of pharmacologically relevant parameters such as the *in vivo* potencies, the maximal drug effects or the turnover rates [90,95] (Figure 2, 3).

7.2.4 Multi-tissue biomarker evaluation

Drug concentrations and endogenous metabolites must be analyzed in multiple biofluids, such as plasma, brain$_{ECF}$, and CSF to understand how the plasma metabolic phenotype relates to the target site effect (Figure 4).

7.2.5 Generate proof of principle for an integrated PK/PD-metabolomics approach in translational CNS drug development

A primary challenge will be the generation of proof of principle for the integrated PK/PD-metabolomics approach.

First of all, multiple same-in-class drugs are to be compared biochemically using a pharmacometabolomics approach. Haloperidol and clozapine showed different efficacy on basis of a multivariate analysis with 58 different components of movement, as well as a multivariate evaluation with monoamines [66]. Although both analyses marked the fact that haloperidol and clozapine showed different efficacy, the pattern was not similar for the behavioral and the monoamine analysis. This indicates two things: 1) a multivariate biochemical is promising with regard to understanding differences between same-in-class drugs. 2) The abovementioned analysis showed that the monoamine based evaluation, although recognizing the pharmacological complexity, still is oversimplified to explain the behavioral outcome.

A second aspect that needs to be included to provide proof of principle is the application of longitudinal metabolomics in multiple species, including humans. Taking into account the known species-differences, the interspecies metabolomes should be compared to understand and map species differences and evaluate applicability of pharmacometabolomics in translational CNS drug development [73]. In particular, it will be important to validate the scaled PK/PD models in humans.

A third aspect is to relate the metabolic fingerprint to relevant clinical (side) effects. Kaddurah-Daouk *et al.* [70] nicely showed this for risperidone, olanzapine and aripiprazole, comparing their lipidomic profiles. Interestingly, aripiprazole showed less impact on lipids, which was associated with the absence of weight gain as a side effect. Further studies will indicate whether such approach is generally applicable in drug development.

7.3 The future of translational CNS drug development with an integrated PK/PD-metabolomics approach

It is envisioned that the integration of PK/PD and pharmacometabolomics will increase the understanding of system-wide pharmacology and improve the interspecies translation of CNS drugs. Specifically, it is envisioned to enable the extraction of system-wide pharmacologically relevant parameters that can be scaled to humans. Additionally, information on biomarkers and pathways is obtained. This advancement must be seen together with the developments in the field of QSP [91,96,97]. The integrated PK/PD-metabolomics approach reveals a PK/PD fingerprint biomarker representing the dynamics of known and unknown pathways. QSP aims to connect the cellular pathway response with the organ- or system-level response. On one hand, the integrated PK/PD-metabolomics approach can thus inform QSP models on relevant pharmacological pathways. On the other hand, QSP models can identify the mechanistic relationship between the single metabolites described by an integrated PK/PD-metabolomics model.

Altogether, an integrated PK/PD-metabolomics approach is envisioned to have a promising role in translational CNS drug development by providing a method to scale system-wide effects from animal to men (Figure 2).

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