Drug Discovery Today: Disease Models
Vol. xxx, No. xx 2017

Systems pharmacology of hepatic metabolism in zebrafish larvae

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Interspecies translation of pharmacological processes needs to improve to reduce attrition in drug development. Systems pharmacology integrates systems biology and pharmacometrics to characterise and quantify system-specific behaviour upon exposure to drugs in different species. The zebrafish is a suitable vertebrate model organism for systems pharmacology, combining high-throughput potential with high genetic homology to higher vertebrates. Zebrafish larvae have been increasingly used for drug screens, but the influence of internal drug and metabolite exposure is hardly studied. Quantifying this internal exposure is essential for establishing both exposure-response and dose-exposure relationships, needed for translation. The zebrafish may also serve as a suitable model species for translational studies on the occurrence of hepatotoxicity and the influence of hepatic dysfunction on drug metabolism.

Section editor: Adriano M. Henney – Avicenna Alliance for Predictive Medicine.

Introduction

Drug development is a complex and costly process with high attrition. Of the terminated drug candidates, the majority fails because of lack of efficacy and safety [1,2]. Efficacy and safety are tested in preclinical experiments, but to improve success rates, interspecies translation needs to move from an empirical to a mechanistic approach [3]. Systems pharmacology is such an approach, combining the strengths of systems biology and pharmacometrics [4]. Understanding the systems of species and their differences helps improving interspecies translation of efficacy and safety data. In this review, we will focus on systems pharmacology of hepatic function and dysfunction, and the importance of understanding the drug exposure over time in a biological system. The unique position of zebrafish larvae as vertebrate model organism for systems pharmacology with high-throughput potential will be discussed.

Systems pharmacology: integrating pharmacometrics and systems biology

Systems pharmacology is a method to contribute to translational medicine by integrating modelling and simulation

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 http://dx.doi.org/10.1016/j.ddmod.2017.04.003

Please cite this article in press as: van RC, et al. Systems pharmacology of hepatic metabolism in zebrafish larvae, Drug Discov Today: Dis Model (2017), http://dx.doi.org/10.1016/j.ddmod.2017.04.003

with data from both preclinical and clinical experiments in a 'systems level' mechanistic way, improving interspecies translation of relevant biological processes [5]. Systems pharmacology originates from two established fields, pharmacometrics and systems biology, and aims to quantify the pharmacological perturbations of the biological system of an organism to improve our understanding of the interaction between a drug and a particular biological system.

Pharmacometrics aims to predict drug effects using mathematical models to quantify interactions between organisms and pharmaceutical compounds [6]. This results in pharmacokinetic-pharmacodynamic (PK-PD) models integrating drug pharmacokinetics, which describes drug exposure as concentration versus time, and drug pharmacodynamics, which describes effects versus drug concentration. A schematic of a PK-PD model can be seen in Fig. 1. Observed outcome measures (i.e. concentrations and effects) are described by mathematical equations, from which the underlying primary model parameters are derived. After evaluation of the predictive performance of a model, the model can be used for predictions and to improve interspecies translation of drug pharmacokinetics and pharmacodynamics and to design treatment regimens in both preclinical and clinical studies [7].

Systems biology studies the structure and dynamics of integrated biological systems to understand processes that are too complex to intuitively comprehend by studying its isolated elements only. Like pharmacometrics, this requires quantitative data as well as advanced computational modelling [8]. Systems biology as holistic approach has the advantage of placing part of a system in the biological context of a complete organism. Characterising individual parts of the system, like gene or protein function, from *in vitro* experiments is an important first step [8]. The next step is to elucidate the interaction of these parts in the network of the whole system. This is relevant in for example disease models, as most diseases are not – as previously believed – caused by a single target, for which a single drug can be designed [9]. In contrast to *in vitro* experiments with human cells only, an *in vivo* whole organism experiment can identify compounds able to treat or cure such a disease [10]. Using these complementary experimental data to inform the systems biology model, the understanding of the biological processes in the organism improves, and with it the understanding of how systems differ between species. This may improve interspecies translation.

Zebrafish larvae as vertebrate model organism in drug development

Systems biology models have been developed in invertebrate organisms, such as yeast (*Saccharomyces cerevisiae*), roundworms (*Caenorhabditis elegans*) and fruit flies (*Drosophila*) [11]. These small organisms are easily genetically modified and allow for high-throughput measurements [11]. However in pharmacological studies, a vertebrate species is believed to have improved translational potential due to its increased genetic homology to mammals. The zebrafish (*Danio rerio*) is such a vertebrate model organism that is increasingly used as a model for biomedical studies [12]. Most genes coding for essential proteins such as those in xenobiotic metabolism are evolutionary conserved. Of human and murine genes, 70% and 71% respectively have a zebrafish orthologue [13]. For comparison, 83% of human genes have a murine orthologue [13]. When considering genes for which defects can cause

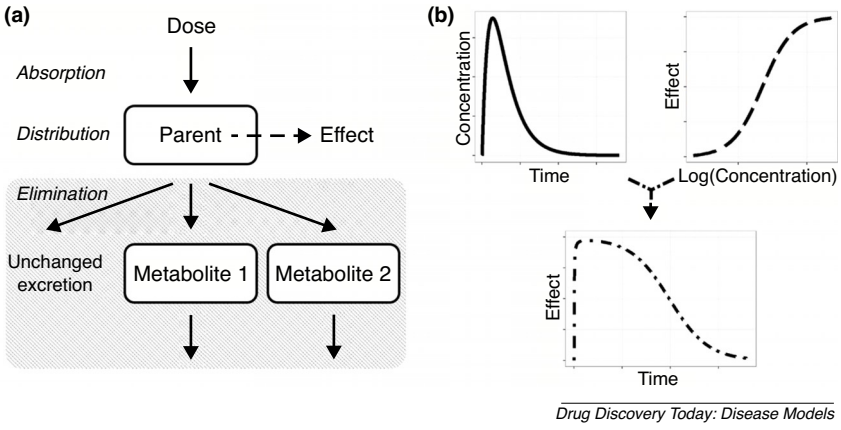

Figure 1. Pharmacology of a parent compound described by a compartmental pharmacokinetic model and a sigmoidal pharmacodynamic model. Panel A. Schematic representation of a compartmental model with absorption, distribution, and elimination by means of metabolism and unchanged excretion, describing the pharmacokinetics of the compound (PK, solid lines in panel B). The concentration of the parent compound drives the effect, in a sigmoidal pharmacodynamic relationship (PD, dashed line in panel B). The PK model becomes more mechanistic when including information on different elimination pathways for example metabolite formation and excretion (grey box); these system-specific properties improve translation of clearance between species. Integrating pharmacokinetics and pharmacodynamics in panel B yields the effect over time profile.

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