Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Systems Biology

Quantitative systems pharmacology and the personalized drug–microbiota–diet axis

Ines Thiele, Catherine M. Clancy, Almut Heinken and Ronan M. T. Fleming

Abstract

Precision medicine is an emerging paradigm that aims at maximizing the benefits and minimizing the adverse effects of drugs. Realistic mechanistic models are needed to understand and limit heterogeneity in drug responses. While pharmacokinetic models describe in detail a drug's absorption and metabolism, they generally do not account for individual variations in response to environmental influences, in addition to genetic variation. For instance, the human gut microbiota metabolizes drugs and is modulated by diet, and it exhibits significant variation among individuals. However, the influence of the gut microbiota on drug failure or drug side effects is under-researched. Here, we review recent advances in computational modeling approaches that could contribute to a better, mechanism-based understanding of drug–microbiota–diet interactions and their contribution to individual drug responses. By integrating systems biology and quantitative systems pharmacology with microbiology and nutrition, the conceptually and technologically demand for novel approaches could be met to enable the study of individual variability, thereby providing breakthrough support for progress in precision medicine.

Addresses

University of Luxembourg, Luxembourg Centre for Systems Biomedicine, Esch-sur-Alzette, Luxembourg

Corresponding author: Thiele, Ines (ines.thiele@uni.lu)

Current Opinion in Systems Biology 2017, **4**:43–52

This review comes from a themed issue on **Pharmacology and drug discovery (2017)**

Edited by **Lars Kuepfer and Tobias Bollenbach**

For a complete overview see the Issue and the Editorial

Available online 10 June 2017

http://dx.doi.org/10.1016/j.coisb.2017.06.001

Keywords

Precision medicine, Pharmacokinetic modeling, Constraint-based modeling, Drug metabolism, Gut microbiota.

Introduction

The effect of drug treatment varies significantly among individuals, and genetic differences alone are insufficient to explain the observed inter-individual differences in drug response [1]. Human gut microbes metabolize many drugs [2]; however, their contribution to an individual's drug response and safety is poorly understood. Diet also modulates the microbiota composition and biochemical functions and alters drug bioavailability. Recent technological advances have led to a greater understanding of the diversity and abundance of gut microbial species. Consequently, research focus is shifting toward exploring the effects of a person's microbiota on metabolism and drug metabolism. Accordingly, constraint-based computational models have been applied to investigate how the gut microbiota can modulate the human metabolic phenotype [3]. In parallel, pharmacokinetic models are used to predict drug responses at the whole-body level [4].

Despite these advances, computational modeling efforts have yet not considered the joint effects of human gut microbiota metabolism, drug metabolism and diet. Consequently, neither the pharmaceutical industry nor academic researchers can properly exploit the increasing knowledge on the human gut microbiota as well as microbiota- and diet-related interpersonal variability for drug development and clinical trial design. The application of statistical methods to genomic or clinical data in pharmacogenomics has been of limited use for patient and therapeutic stratification [5] and does not provide a mechanistic system-level understanding of the targeted biological systems. Another limitation of pharmacogenomics is its failure to integrate exogenous factors that alter drug bioavailability, such as the human gut microbiota or diet [6].

Human and microbial drug metabolism

Individual drug response. Variations in individual treatment responses pose a major challenge to health professionals and patients as well as to drug development and clinical trial design [7]. Front-line physicians must therefore adapt a pragmatic or empirical prescription decision tree until an effective therapy for each patient is identified. Furthermore, the adverse drug reactions that may ensue are ranked among the top 10 causes of morbidity and mortality in the developed world [8]. Certain adverse effects are related to the production of toxic drug metabolites [9], and both the duration and extent of pharmacological action are related to the rate of drug metabolism [10]. Pharmacogenomic studies have greatly improved our understanding of individual variations in drug metabolism caused by genetic individuality [11]. However, these studies cannot explain the large

observed individual variability in drug response as they only focus on the genetic variability of drug-metabolism related genes. Consequently, variation in a person's physiology, such as gender, ethnicity, body mass index, should be considered. Moreover, environmental factors, such as diet, gut microbiota composition, exercise, and stress, can modulate a person's metabolic phenotype and drug metabolism. As these factors can significantly alter drug efficacy and safety profiles [12], they must be accounted for in drug development and treatment.

Gut microbial drug metabolism. The human gut microbiota is a metabolically active community of 10–100 trillion commensal, pathogenic, and symbiotic organisms composed of 500–1000 species and including two to four million different genes [13,14]. The gut microbiota contributes to the essential functions of the human host, such as food digestion, essential amino acids and vitamin synthesis, pathogen protection, and host immune system maturation [15]. The gut microbiota has also emerged as a significant factor influencing drug response [2]. Gut microbes affect drug efficiency both directly and indirectly. In turn, exposure to antibiotics and host-targeted drugs induced changes in gut microbiota gene expression across several phyla [16]. This xenobiotic modulation of microbial gene expression varies between human individuals suggesting a gut microbiota-dependent personalized drug response [16]. At least 30 host-targeted drugs are directly affected by gut microbial activity [17,18] (Figure 1), yet mechanistic insight in the effects on drug efficiency and safety is often lacking [19].

Direct microbial effects on drugs include chemically modifying drug structures, binding to drugs, and degrading drugs [17,20]. The gut microbiome encodes enzymes that perform drug transformations, including reduction, acetylation, deacetylation, and demethylation [17]. In certain cases, these transformations result in the desired conversion of a prodrug to an active drug. For example, the prodrug sulfasalazine, a treatment for inflammatory bowel disease, is cleaved into the active drug 5-aminosalicylic acid by intestinal microbial azoreductases [17]. However, in other cases, the drug is inactivated or converted into a more toxic form (Figure 1). For example, the cardiac drug digoxin is inactivated by the cardiac glycoside reductase of *Eggerthella lenta* [21]. This undesirable inactivation can be reduced by increasing the amount of dietary arginine, demonstrating that dietary interventions can influence drug–microbiota interactions [21]. Only *E. lenta* strains carrying the "cardiac glycoside reductase" (*cgr*) operon carry out this biotransformation. The abundance of cardiac glycoside reductase in stool samples has been shown to predict digoxin inactivation and the resulting reduction in drug activity [21,22]. This example clearly demonstrates that genomic and transcriptomic analyses of the gut microbiota can be useful for predicting drug responses [12,16].

Additionally, gut microbes can indirectly affect the drug response and toxicity by the production of microbial metabolites. One example is the gut microbial production of p-cresol that competes with acetaminophen (paracetamol) for sulfonation by a liver enzyme and thus contributes to drug toxicity in certain individuals [10]. To date, few mechanistic insights have been provided for the effects of drug–microbiota interactions, including drug efficacy and safety, and the species capable of drug transformations are largely unknown [17]. Moreover, the gut microbiota is characterized by functional redundancy, i.e., the same functions can be performed by multiple bacteria that may be either closely or distantly related [23]. This redundancy also extends to drug-metabolizing genes in multiple species across phyla. Hence, a microbiota-wide systematic approach to exploiting and characterizing the capabilities of the gut microbiota to modulate drug metabolism is urgently required.

Computational modeling approaches

Pharmacokinetic models quantitatively describe the absorption, distribution, metabolism and elimination (ADME) of a drug to predict the time course of a drug's concentration in the body [24,25]. In particular, physiologically based pharmacokinetic (PBPK) models, which compose the core of quantitative systems pharmacology [26,27], describe whole-body drug kinetics by using ordinary differential equations and an organ compartment structure [28,29] (Figure 2). These models contain system-specific and drug-specific parameters. The system-specific parameters include blood flow, organ volumes, enzyme and transporter expression, and plasma protein concentrations [30]. The drug-specific parameters include intrinsic clearances, volume of distribution, solubility and physicochemical parameters, tissue partitioning, plasma protein binding affinity, and membrane permeability [30]. The drug-dependent parameters allow for the mechanistic extrapolation of human pharmacokinetics from *in vitro* and in silico data via a "bottom-up" approach [31]. Whole-body PBPK models have been published for at least 50 drugs [32–34], including 32 with an advanced compartment absorption and transit model (ACAT). The ACAT model [35] was based on a CAT model [36], which did not consider the dissolution of solid particles. The ACAT model considers nine gastrointestinal compartments, being the stomach, seven small intestinal segments, and the large intestine. It represents pH-dependent drug solubility, controlled release, drug absorption by the stomach and colon, metabolism in the gut or liver, degradation in the lumen, changes in absorption surface area, changes in drug transporter densities, and changes in efflux