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REVIEW

The effects of fasting on drug metabolism

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ABSTRACT

Introduction: There is considerable variability in the rates and extent of drug metabolism between patients due to physiological, genetic, pharmacologic, environmental and nutritional factors such as fasting. This variability in drug metabolism may result in treatment failure or, conversely, in increased side effects or toxicity. Preclinical studies have shown that fasting alters drug metabolism by modulating the activity of drug metabolizing enzymes involved. However, until recently little was known about the effects of fasting on drug metabolism in humans.

Areas covered: This review describes the effects of fasting on drug metabolism based on both preclinical studies and studies performed in humans.

Expert opinion: A better understanding of the effects of fasting may improve the efficacy and safety of pharmacotherapy for individual patients. Fasting contributes to variability in human drug metabolism by differentially affecting drug metabolizing enzymes. Although the effects of fasting on drug metabolism appear to be small (between 10-20%), fasting may be relevant for drugs with a small therapeutic range and/or in combination with other factors that contribute to variability in drug metabolism such as physiological, genetic or pharmacological factors. Therefore, additional research on this topic is warranted.

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Drug Metabolism; Fasting; Nutrition; Pharmacokinetics; Personalized medicine

1. Introduction

One out of five hospital admitted patients in The Netherlands is malnourished [1]. These include patients with an extreme low body weight, such as anorectic patients, but also patients suffering from significant weight loss in a relatively short period of time. This latter condition is often seen in geriatric or oncological patients [2,3]. In these patient groups the prevalence is even higher: 38% and 33% respectively. Although different types of malnutrition can be distinguished, they all result in a fasting related response of metabolic changes, especially in fat and glucose metabolism [4]. Moreover, fasting can also contribute to variability in drug disposition which may result in treatment failure, increased side effects or even toxicity [5].

The disposition of drugs in patients can be described by four basic processes: **a**bsorption, **d**istribution, **m**etabolism and **e**xcretion (ADME) [5]. In addition to the administered dose, the net effect of these four processes determines the plasma drug concentration. In general, it is important that the plasma concentration is within a therapeutic range to achieve safe and effective drug treatment. If the drug concentration is below this range, the drug may be ineffective, whereas if drug concentration exceeds this range, toxicity may occur [5]. There are many factors that contribute to variability in drug disposition. These factors include patient characteristics (e.g. age and body weight), genetic, physiologic, pharmacologic (e.g. drug-drug interactions due to concomitant use of other medication), environmental factors and nutritional status, such as fasting (Figure 1) [6]. More specifically, these factors also contribute to variability in drug metabolism. Although studies on the effect of fasting on bioavailability are often included in drug registration trials [7], less is known about the effect of fasting on drug metabolism. To gain more insight in the effects of fasting on drug metabolism, this review focusses on both preclinical studies and studies in humans performed in this field.

2. Drug metabolism

Drug metabolism is the metabolic breakdown of drugs which is catalyzed by drug metabolizing enzymes and consists of two phases, phase I and II. In phase I, reactive and polar groups are introduced into drug substrates by oxidation, reduction or hydrolysis [8]. Cytochrome P450 (CYP) enzymes play an important role in phase I drug metabolism because of their ability to catalyze the oxidative biotransformation of most drugs [8]. CYP enzymes are microsomal enzymes which are abundantly present in the liver, gastrointestinal tract, kidney and lungs [9]. This superfamily of enzymes consists of families and subfamilies of enzymes classified based on their amino acid sequence. In humans, five CYP isoforms predominantly present in the liver are frequently involved in drug metabolism: CYP1A2, CYP2D6, CYP2C9, CYP2C19 and CYP3A4 [6]. Together, these isoforms are responsible for more than 70% of all phase I dependent metabolism of drugs [6].

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Article highlights

- Fasting contributes to variability in drug metabolism.
- Preclinical studies revealed effects of fasting on the activity of enzymes involved in phase I and II drug metabolism.
- In humans, fasting affects drug metabolizing enzyme activity in a non-uniform pattern.
- Fasting is part of a complex interplay of factors affecting drug response (e.g. patient characteristics, genetic, physiologic, pharmacologic and environmental factors).
- Knowledge of the effects of fasting contributes to personalized medicine in which drug therapy is tailored to the individual patient and drug response can be predicted accurately leading to optimized health care.

This box summarizes key points contained in the article.

In phase II, the drug metabolites formed in phase I are conjugated with endogenous molecules such as glucuronic acid or glutathione [10]. These metabolites become more polar which enhances further renal or biliary excretion. The phase II metabolizing or conjugating enzymes consist of many superfamilies of enzymes including uridine diphosphate-glucuronosyltransferases (UGTs) involved in glucuronidation of drugs, sulfotransferases (SULTs) involved in sulfation of drugs and glutathione-*S*-transferases (GSTs) involved in the conjugation of the reduced form of glutathione (GSH) to the drug [9]. UGTs represent the majority of phase II metabolizing enzymes. UGT catalyzes the transfer of glucuronic acid from UDP-glucuronic acid to various acceptor substrates including bile acids, bilirubin, steroid hormones and drugs [11]. Approximately 10% of the top 200 prescribed drugs are glucuronidated by UGTs [12]. These enzymes represent two families (UGT1 and UGT2) including 9 human family UGT1 enzymes, 3 subfamily UGT2A and 8 UGT2B enzymes [13]. UGT1A1 is the most familiar UGT isoform because of its important role in bilirubin conjugation. Genetic variants have shown to decrease UGT1A1 enzyme activity which can lead to jaundice as for the syndromes of Gilbert and Crigler-Najjar [11]. Furthermore, impaired UGT1A1 enzyme activity is associated with toxicity of the oncolytic agent irinotecan [14]. UGT1A1 is also involved in acetaminophen (paracetamol) metabolism [15]. In addition to UGT1A1, other UGT isoforms are important in drug metabolism [11]. For example UGT1A4, UGT2B4 and UGT2B7 which are involved in the metabolism of midazolam [16].

Sulfotransferases (SULTs) enable the transfer of a sulfonate group ($-SO^{3-}$) from the cofactor 3′-phosphoadenosine-5′-phosphosulfate to a substrate [17]. These enzymes can conjugate with a broad range of xenobiotic substrates and drugs (e.g. acetaminophen) but also with endogenous substrates such as steroids, catecholamines, and thyroid hormones [18].

The most important biological function of glutathione-*S*-transferases (GSTs) is defense against reactive and toxic electrophiles such as reactive oxygen species (ROS) that arise through normal metabolic processes [10,19]. Many of these ROS are formed by oxidative reactions catalyzed by CYP enzymes (phase I drug metabolism). For example, a small percentage (5%-10%) of acetaminophen is converted by CYP enzymes to the reactive and hepatotoxic metabolite *N*-acetyl-*p*-benzoquinone-imine (NAPQI) [20]. NAPQI can be detoxified by GST-mediated conjugation with endogenous glutathione to nontoxic metabolites [20].

3. Fasting and drug metabolism

3.1. Animal studies

Preclinical studies have shown that fasting can alter phase I and phase II drug metabolism by modulating the activity of the different enzymes involved [21]. Already in 1965, Kato and Gillette established that fasting enhances the activity of

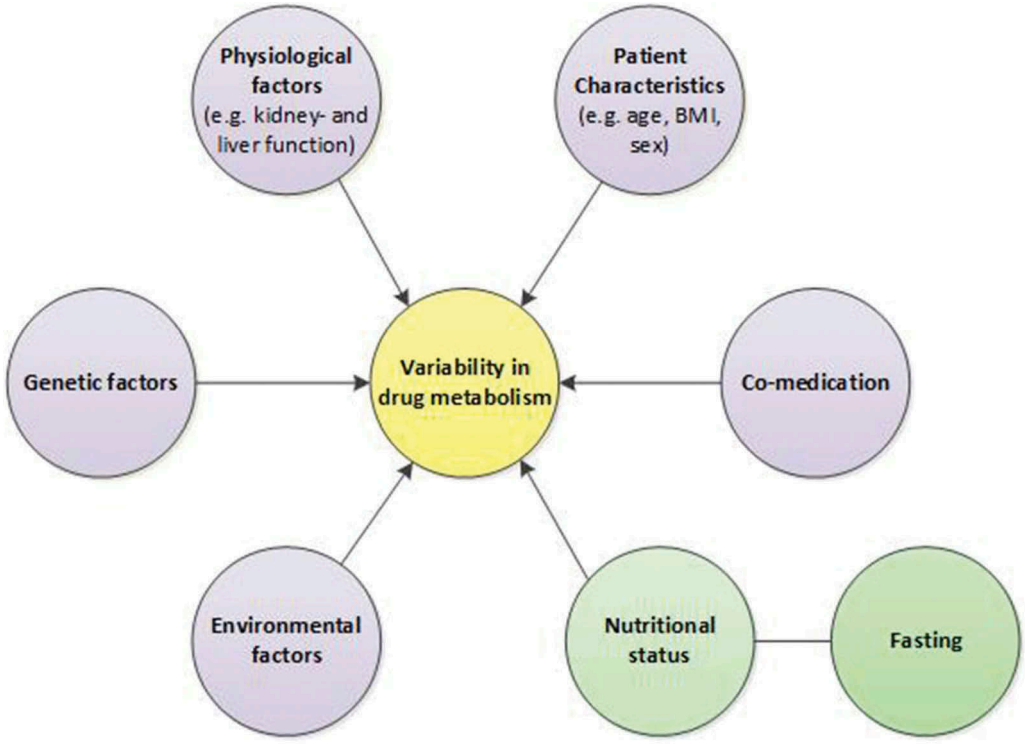

Figure 1. Factors that contribute to variability in drug metabolism.

'almost all' drug metabolizing enzymes in liver microsomes in female rats [22]. Later studies have shown that starvation of rats increased demethylation of dimethylnitrosamine which is mediated by hepatic Cyp2e1 [23]. Starvation of rats for 3 days also resulted in a doubling of total CYP levels in the kidney [24]. In contrast with this upregulation of CYP enzymes, the male-specific isoform Cyp2C11 was down-regulated by starvation in the liver of rats. Similarly, Cyp2C13 and b2 levels were down-regulated by fasting [25,26]. Fasting can also affect phase II drug metabolism. For example, Xu *et al*. have shown that fasting increased hepatic UGT isoforms Ugt1a1, −1a6, −1a7, −1a9, −2b1, −2b5, −2a3, −3a1, and −3a2 mRNA expression in mouse liver [27]. Furthermore, Ding *et al*. have shown that fasting induces expression of genes encoding CYP enzymes (Cyp2b10), UGT (Ugt1a1) and SULT (Sult2a1) in mice liver [28]. On the other hand, Tsuchiya *et al*. have recently shown that fasting did not affect UGT (Ugt1a6) nor SULT (Sult1a1) in rat liver [29]. In their study the expression of drug metabolizing enzyme genes and total glutathione content which are involved in acetaminophen metabolism were examined in rats after normal feeding and fasting conditions. The fasted rats showed significantly higher expression of Cyp2e1, the gene encoding the enzyme that metabolizes acetaminophen to its toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) [29]. They also had lower levels of liver total glutathione, which detoxifies NAPQI. In contrast, the gene expression of UDP-glucuronosyltransferase 1A6 (Ugt1a6), sulfotransferase 1A1 (Sult1a1), and glutathione S-transferase M1 (Gstm1) was not affected by fasting [29].

The discrepancies between studies in effect of fasting on the expression of drug metabolizing enzyme genes may be due to interspecies differences [30]. Although sequence homology of Cytochrome P450 enzymes among species is high, small differences in amino acid sequences at the active sites of CYP enzymes can result in profound differences in isoform-catalyzing metabolism and specificity of the drugs they metabolize. Therefore, fasting may not exhibit the same selectivity for human CYP isoforms as for the corresponding animal isoforms [29]. Nonetheless, similarities are present for some specific drug metabolizing enzymes, for example Cyp1a2 and Cyp2c11 in male rats which may be used to study the effects of fasting on the corresponding enzymes CYP1A2 and CYP2C9 in humans [31]. However, this is something to bear in mind when interpreting preclinical results for translation to the clinical setting.

The effects of fasting on drug metabolizing enzymes in experimental models can be explained in part by altered activity of nuclear transcription factors. The nuclear receptors pregnane X receptor (PXR) and constitutive androstane receptor (CAR) serve as xenosensors, which regulate the activity of many of the drug metabolizing enzymes in animals [32,33]. Interestingly, animal studies have shown that short-term fasting defined as the abstinence of food and drinks except water for a period of 24 to 72 hours, can increase drug metabolizing enzyme activity by activation of nuclear receptors such as the pregnane X receptor (PXR) and the constitutive androstane receptor (CAR) [28,33].

Fasting increases cyclic adenosine monophosphate (cAMP) and activates protein kinase A (PKA), which in turn induces peroxisome proliferator-activated receptor coactivator-1α (PGC-1α) [28]. PGC-1α then interacts with hepatocyte nuclear factor-4α and induces CAR after which CAR induces CAR target genes [33]. This is a physiologically relevant response, since CAR-deficient mice are defective in fasting adaptation and lose more weight during prolonged fasting [28]. Compared to CAR, PXR is activated by a larger variety of endogenous and exogenous compounds including steroids (e.g. progesterone, corticosterone, dexamethasone), antibiotics (e.g. rifampicin), antimycotics, bile acids and many herbal compounds [33,34]. Experimental studies have also demonstrated that fasting activates PXR in mice liver [35]. In accordance, fatty acids, which increase readily during short-term fasting due to increased lipolysis of triglycerides in adipose tissue, activate CAR and to a lesser extend PXR [36]. To investigate whether fasting-induced alterations in CYP mediated drug metabolism are mediated by CAR, De Vries *et al*. used a drug cocktail validated in humans consisting of five drugs as probes for specific P450 enzymes: caffeine (CYP1A2), metoprolol (CYP2D6), omeprazole (CYP2C19), midazolam (CYP3A4) and *s*-warfarin (CYP2C9) [31,37]. The drugs were simultaneously administered to wild type (WT, C57Bl/6) mice or mice deficient for CAR ($CAR^{-/-}$) that were either fed ad libitum or fasted for 24 hours. Blood was sampled at predefined intervals and drug concentrations were quantified. Furthermore hepatic mRNA expression of orthologous P450 enzymes (Cyp1a2, Cyp2d22, Cyp3a11, Cyp2c37, Cyp2c38 and Cyp2c65) were measured [30,38]. The results showed that the absence of CAR was associated with a decrease in metabolism of omeprazole, metoprolol and midazolam in fed mice. However, these fasting-induced alterations in CYP mediated drug metabolism were largely independent of CAR [31]. Interestingly, the study of De Vries *et al*. also demonstrated a differential effect of fasting on drug metabolizing enzyme expression. Fasting increased Cyp3a11 and Cyp2c38 expression but decreased Cyp1a2 and Cyp2d22 expression in both WT and $CAR^{-/-}$ mice [31].

3.2. Human studies

Until recently the role of fasting on drug metabolism in general, and on individual enzyme activities in particular, had hardly been studied in humans. Nonetheless, the activities of CAR and PXR are increased by fasting as shown by preclinical studies. Since both transcription factors are involved in the regulation of phase I and II drug metabolizing enzymes in animals, it is hypothesized that fasting may contribute to both intra- and inter-individual variations in human drug metabolism as well [21,39]. Moreover, fasting related consequences, such as weight loss or cachexia, are common in patients. For example, the prevalence of cachexia ranges from about 10% in patients with chronic heart failure or COPD to approximately 70% in patients with advanced cancer [40]. Considering the experimental data, changes in drug metabolism due to alterations in nutritional conditions such as fasting may potentially alter the concentration of drugs in humans, resulting in treatment failure, or, conversely, in untoward side effects.

A few clinical studies have been performed studying the role of short-term fasting, defined as the abstinence of food and drinks except water for a period of 24 to 72 hours, on drug metabolism. Data on the effects of longer periods of

fasting are scarce, probably due to ethical reasons. However, it should be realized that a major part of the metabolic features of the fasting response can be readily stimulated, for example by only skipping breakfast and lunch in humans [32]. Therefore, a short-term (24 to 72 hours) period of fasting can well be used to study the effects of fasting on drug metabolism. In 1994, O'Shea *et al*. studied the effect of short-term (36 hours) fasting on CYP2E1 probe chlorzoxazone [41]. O'Shea *et al*. have shown that fasting resulted in a reduction in the oral clearance of chlorzoxazone which, however, was in contrast with previous findings in rats demonstrating that CYP2E1 levels were induced by fasting [41]. The authors discussed that this may reflect an interspecies difference in CYP2E1 regulation, but concluded that it more likely reflects degradation of the enzyme by lipid peroxidation resulting from the prolonged period of fasting.

3.3. Fasting differentially affects drug metabolizing enzymes

To gain more insight in the effects of fasting on the activity of enzymes involved in drug metabolism, we performed a randomized controlled crossover study in healthy subjects. In order to study only the effect of fasting on drug metabolism instead of a combined effect of various factors, the effect of fasting on human drug metabolism was examined in crossover designed trials in which each subject served as its own control. Furthermore, subjects were randomly assigned for the order of the interventions: an overnight fast after a regular diet (control) versus 36 hours of fasting (short-term fasting). Subjects received a single administration of a Cytochrome P450 cocktail consisting of enzyme selective probe drugs. Each probe is selective for an individual drug metabolizing enzyme whereby changes in concentrations of the probe drug reflect changes in drug metabolizing enzyme activity. Therefore, probes are commonly used as phenotyping strategy in drug development to study drug-drug interactions but probes are also used as well-established method to study enzyme activity in humans [42]. The cocktail was administered orally and intravenously after an overnight fast (control intervention) and after 36 hours of fasting administered and consisted of caffeine (CYP1A2), metoprolol (CYP2D6), midazolam (CYP3A4), omeprazole (CYP2C19) and warfarin (CYP2C9) [37,43]. We found that short-term (36 hours) fasting increased systemic clearance of caffeine and metoprolol by respectively ~17% ($p = 0.04$) and ~13% ($p < 0.01$). This indicates that fasting increased the activity of CYP1A2 and CYP2D6, considering that caffeine and metoprolol are probes for the activity of these enzymes, respectively. Furthermore, short-term fasting decreased systemic S-warfarin clearance (19%, $p < 0.01$) which indicates decreased activity of CYP2C9, considering that S-warfarin is a probe of CYP2C9 activity (Table 1) [43].

We also studied the effect of fasting on midazolam and its metabolites [44]. Midazolam is primarily (≈ 95%) metabolized by CYP3A4 to 1-OH-midazolam which makes the drug a suitable probe for isoform CYP3A4 [45,46]. After oxidative hydroxylation, the 1-OH-metabolite is predominantly metabolized by UGT2B4/2B7 to 1-OH-midazolam-*O*-glucuronide (phase II drug metabolism) to enable urinary excretion [16].

Table 1. Effects of short-term fasting (36 hours) on human drug metabolizing enzymes.

Human drug metabolizing enzyme	Enzyme activity *% increase (↑) or % decrease (↓) compared to control**
CYP1A2	↑ 17% ($p = 0.04$)
CYP2C9	↓ 19% ($p < 0.01$)
CYP2C19	*No effect*
CYP2D6	↑ 13% ($p < 0.01$)
CYP3A4	↑ 12% ($p < 0.01$)
UGT1A4/2B4/2B7	↓ 13% – 20% ($p < 0.01$)

* *Enzyme activity after short-term Fasting (36h) compared to control (overnight fast) as measured using probe drugs in human subjects.*

Our results show that short-term (36 hours) fasting increased CYP3A4 mediated systemic midazolam clearance (12%, $p < 0.01$), which indicates that fasting increased the activity of CYP3A4. Furthermore, short-term fasting decreased the apparent clearances of 1-OH-midazolam (13%, $p < 0.01$) and 1-OH-midazolam-O-glucuronide (20%, $p < 0.01$), which indicates decreased UGT-mediated metabolism due to fasting (UGT1A4, UGT2B4/2B7) (Table 1) [44].

Although most of the preclinical studies suggest that short-term fasting increases the activity of nuclear receptors CAR and PXR, thereby increasing the activity of drug metabolizing enzymes, the clinical studies described above demonstrate that short-term fasting differentially affects enzymes which are important in human drug metabolism [28,33]. Short-term fasting increases the activity of phase I drug metabolizing enzymes CYP1A2, CYP2D6 and CYP3A4 (reflected by increased systemic clearances of caffeine, metoprolol and midazolam, respectively) whereas it decreases the activity of CYP2C9 (reflected by decreased *S*-warfarin clearance) [43,44,47]. Regarding phase II drug metabolizing enzymes, short-term fasting decreases UGT1A4/2B4/2B7 mediated (midazolam) metabolism [44]. Based on these findings fasting induced regulation of drug metabolizing enzymes seems to be more complex than expected from preclinical research and possibly consists of (multiple) positive and negative feedback loops. Additional research is recommended to further establish the molecular and pharmacological mechanisms underlying our observations and the clinical implications of our findings.

4. Expert opinion

The studies presented above demonstrate that short-term fasting contributes to variability in drug metabolism. However, the effects of fasting found appear to be small (between 10–20%, Table 1). For most drugs these effects of fasting found within subjects are much smaller than the between-subject (interindividual) variability in drug metabolism [48]. Nevertheless, this might be relevant for patients with fasting related consequences such as weight loss and cachexia using drugs with a small therapeutic range and/or in combination with other factors that contribute to variability in drug metabolism such as patient characteristics, genetic, physiologic or pharmacologic factors. Examples of drugs with a small therapeutic range which are metabolized by enzymes affected by short-term fasting are certain antidepressants (e.g., amitriptyline (CYP2D6/CYP2C19), clomipramine (CYP1A2/CYP2D6/CYP2C19), some atypical antipsychotics (e.g. clozapine (CYP1A2), olanzapine

(UGT/CYP1A2/CYP2D6) and phenytoin (anti-epileptic agent, CYP2C9/CYP2C19) [48–51].

Our findings may also be applicable to oral cytotoxic agents which are commonly used in oncology and extensively metabolized by drug metabolizing enzymes. Many of these cytotoxic agents are approved to be administered at fixed doses [52]. In oncological patients with fasting related problems this flat-fixed dose regimen may theoretically result in treatment failure or, conversely, in toxicity.

4.1. Personalized nutrition

In addition to considering short-term fasting as a factor that contributes to variability in drug response, there is growing evidence for short-term fasting applied as therapy [53]. As for medicine, Hippocrates already advocated the practice of fasting in the 4th century BC, believing that to eat when sick would be to feed the illness. However, it took centuries to obtain a better understanding of nutrition, including fasting, applied as therapy and/or to improve health. Today, research is performed in different fields to personalize nutrition. For example by organizations such as the Dutch organization for applied scientific research (TNO) which collaborates with different parties such as food producers and universities to implement personalized nutrition at large scale because this improves people's health behavior to prevent diseases such as obesity and diabetes [54]. Nutrition also draws significant public attention because diet, together with exercise, remains the mainstay of lifestyle change. Although many diets are not evidence based and often replaced by others shortly after introduction, a promising fasting based diet developed by Longo *et al*. was recently discussed in one of the leading medical journals JAMA [55,56]. Subjects had to restrict their calories by 60% for five consecutive days a month over three months to get the benefits of the so-called 'fasting-mimicking diet'. This diet is based on the interesting hypothesis that post-fasting activates stem cells which drive the health and longevity benefits of this diet [48].

Furthermore, recent studies have shown that short-term fasting can have a positive effect in the treatment of cancer [57–59]. By short-term fasting, the susceptibility to chemotherapy can differ between healthy somatic and cancer cells, a phenomenon called differential stress resistance [57]. It is likely that the effects of short-term fasting will be enhanced if the period of fasting is prolonged, but although easily prescribed, adherence to a fasting protocol will be challenging if not impossible in cases of serious and/or terminal diseases. Therefore, clinical trials are now being performed in the field of oncology with low protein fasting mimicking diets to ease the burden of prolonged fasting [58,60].

4.2. Future perspectives on fasting and drug metabolism

A better understanding of the effects of fasting may improve the efficacy and safety of pharmacotherapy for individual patients. In order to optimize drug treatment in oncology, it would be of interest to further study the effects of low protein diets on differential stress resistance, but also to study the effects of these fasting mimicking diets on the metabolism of the drugs administered during these diets [48]. In particular, research should focus on anti-cancer drugs that are metabolized by phase I or phase II drug metabolizing enzymes which are affected by fasting such as the anti-mitotic cytotoxic agents paclitaxel and docetaxel (CYP3A4) or the topoisomerase inhibitors etoposide (CYP2C9, CYP3A4) and irinotecan (CYP3A4, UGT1A1). Irinotecan is used in the treatment of metastatic colon cancer. It is a prodrug which needs to be metabolized by carboxyl esterase to the active metabolite SN-38 to exert its anti-tumor activity [61]. SN-38 is further metabolized by UGT1A1 to the inactive metabolite SN-38-glucuronide. Irinotecan is not entirely metabolized to SN-38. Another fraction of the drug is directly metabolized by CYP3A4 to inactive metabolites. Previously, Mathijssen *et al* have shown that St. John's wort, which increases CYP3A4 enzyme activity, *in*creases the formation of the CYP3A4-mediated inactive metabolites thereby *de*creasing the exposure of the active metabolite SN-38 [62]. Their findings indicate that patients on irinotecan treatment should refrain from taking this herb. Since short-term fasting increased CYP3A4-mediated clearance of midazolam, fasting may also affect CYP3A4 mediated irinotecan metabolism by decreasing the exposure of the active metabolite SN-38 which may result in treatment failure [44].

Short-term fasting is not the only factor contributing to variability in drug metabolism, but adds to the effects of other factors, including patient characteristics, physiological, pharmacological and genetic factors. Following completion of the Human Genome Project a lot of research has been performed in the era of pharmacogenetics [48]. However, pharmacogenetics alone, and also when studied together with patient characteristics (e.g. age and gender), does not adequately describe all variability in drug responses [63]. Therefore, there is growing interest in so called systems pharmacology which is based on interdisciplinary translational science [63]. Systems pharmacology is an holistic approach to pharmacology that aims to develop a global understanding of the interaction between pathophysiology and drug action in humans to explain, simulate and predict the net clinical drug response [63]. It approaches different factors that contribute to variability in drug metabolism as networks of interaction and uses bioinformatics and statistical techniques (e.g. physiologically based pharmacokinetic models (PBPK)) to integrate and interpret these interactions [63]. Since fasting related consequences such as weight loss or cachexia are common in patients, especially in patients with advanced cancer, additional research should be performed to study the effects of short-term fasting together with other factors known to contribute to variability in drug metabolism by using a systems pharmacological approach.

Increasing knowledge on factors contributing to variability in drug metabolism such as short-term fasting will improve personalized medicine, in which drug therapy is tailored to the individual patient. From a clinical perspective, a valuable tool for tailoring the dose of prescribed drugs to the individual characteristics of a patient is therapeutic drug monitoring (TDM). TDM is based on the measurement and interpretation of drug concentrations in e.g. plasma or serum and aims to improve patient care by adjusting the dose of a drug to achieve concentration

levels within an established therapeutic range [64]. Although this requires the availability of appropriate analytical methods, it can also be used to control compliance which is another, non-physiological, factor contributing to variability in drug response.

5. Conclusion

Fasting contributes to variability in human drug metabolism. Although the effects of fasting appear to be relatively small and may not seem clinically relevant, fasting could be relevant for drugs with a small therapeutic range and/or in combination with other factors that contribute to variability in drug metabolism such as physiological, genetic or pharmacological factors.

Fasting is part of a complex interplay of factors affecting drug response [48]. Knowledge of the effects of fasting contributes to personalized medicine in which drug therapy is tailored to the individual patient and drug response can be predicted accurately leading to optimized health care. Therefore, additional research on this topic is warranted.

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