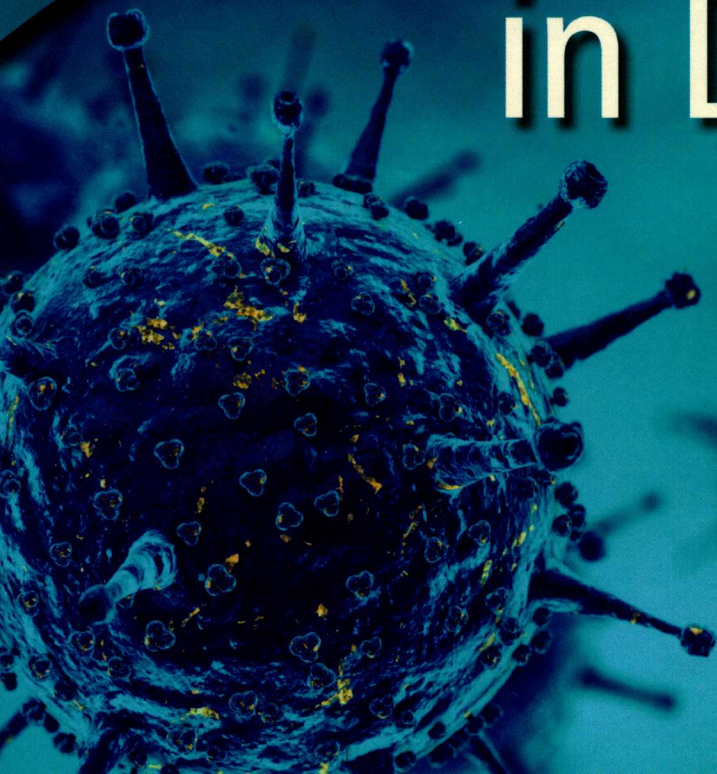Edited by
Wen Xie

Drug Metabolism in Diseases

DRUG METABOLISM IN DISEASES

Edited by

WEN XIE, MD, PhD

Professor of Pharmaceutical Sciences and Pharmacology,
The Joseph Koslow Endowed Chair in Pharmaceutical Sciences,
Director of the Center for Pharmacogenetics School of Pharmacy,
University of Pittsburgh, Pittsburgh, PA, United States

ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO
Academic Press is an imprint of Elsevier

For information on all Academic Press publications
visit our website at https://www.elsevier.com/

Working together
to grow libraries in
developing countries

www.elsevier.com • www.bookaid.org

DRUG METABOLISM
IN DISEASES

Contributors

L.M. Aleksunes Rutgers University, Piscataway, NJ, United States

X. Chai University of Pittsburgh, Pittsburgh, PA, United States; Zhejiang University, Hangzhou, China

J.E. Constance University of Utah, Salt Lake City, UT, United States

J.C. Coons University of Pittsburgh, Pittsburgh, PA, United States

P. Empey University of Pittsburgh, Pittsburgh, PA, United States

L. Gorczyca Rutgers University, Piscataway, NJ, United States

C.A.J. Knibbe Leiden University, Leiden, The Netherlands; St. Antonius Hospital, Nieuwegein, The Netherlands

D. Kojovic University of Toronto, Toronto, ON, Canada

E.H.J. Krekels Leiden University, Leiden, The Netherlands

X. Li Xiangya Hospital Central South University, Changsha, China

Z.Q. Liu Xiangya Hospital Central South University, Changsha, China

P. Lu University of Pittsburgh, Pittsburgh, PA, United States

E.T. Morgan Emory University, Atlanta, GA, United States

J.E. Moscovitz Rutgers University, Piscataway, NJ, United States

T.D. Nolin University of Pittsburgh, Pittsburgh, PA, United States

M. Piquette-Miller University of Toronto, Toronto, ON, Canada

S.M. Poloyac University of Pittsburgh, Pittsburgh, PA, United States

J.E. Rower University of Utah, Salt Lake City, UT, United States

R. Sane Bristol Myers Squibb, Wallingford, CT, United States

C.M.T. Sherwin University of Utah, Salt Lake City, UT, United States

M. Sinz Bristol Myers Squibb, Wallingford, CT, United States

W. Xie University of Pittsburgh, Pittsburgh, PA, United States

S. Zeng Zhejiang University, Hangzhou, China

Preface

I am very happy to present you with this special topic book titled *Drug Metabolism in Diseases*.

Drug metabolism is essential for both drug therapy and drug safety. In addition to the genetic and environmental factors, diseases and physiological states of patients have profound effects on drug metabolism and disposition. Examples of diseases known to affect drug metabolism include liver and kidney diseases, inflammation and sepsis, cardiovascular diseases, and diabetes. Physiological conditions that can affect drug metabolism exist in pediatric and pregnant populations, and patients in critical care, among others. Understanding the patho-physiological effect on drug metabolism will help to guide better and safer use of clinical drugs. Armed with the knowledge of disease effects on drug metabolism, the use of drugs can be tailored to specific diseases or physi-ological conditions, which is highly relevant to personalized medicine and precision medicine. For these reasons, there is a great need for a book in this area. The topics mentioned earlier have been systemically covered in this book.

Another key feature of this book is the mechanistic insights by which diseases and physiological states affect drug meta-bolism. Examples of the mechanistic insights throughout the chapters include pharmacogenetics, xenobiotic receptors, nuclear receptors, transcriptional regulation of genes encoding drug metabolizing en-zymes and transporters, crosstalk between xenobiotic metabolism and endobiotic metabolism, as well as the reciprocal effect of the expression and activity of drug-metabolizing enzymes and transporters on the clinical outcome of diseases. Under-standing these mechanistic insights is paramount in harnessing the benefits of the knowledge communicated in this book and to improve the effective and safe use of drugs in the clinic.

I want to thank all of the contributing authors who are experts in the forefront of this emerging and exciting field of research. Special thanks go to Kristine Jones, Senior Acquisitions Editor at Elsevier, who initially approached me for a book project. I also want to thank Molly McLaughlin, Editorial Project Manager at Elsevier, who has been extremely helpful in all stages of the devel-opment of this book.

Wen Xie, MD, PhD
Professor of Pharmaceutical Sciences and Pharmacology
The Joseph Koslow Endowed Chair in Pharmaceutical Sciences
Director of the Center for Pharmacogenetics
School of Pharmacy
University of Pittsburgh, Pittsburgh, PA

Contents

Introduction of Drug Metabolism and Overview of Disease Effect on Drug Metabolism

R. Sane, M. Sinz

Bristol Myers Squibb, Wallingford, CT, United States

OUTLINE

List of Abbreviations

AAG Alpha-1 acid glycoprotein
ADME Absorption, distribution, metabolism, and elimination
AUC Area under the curve
BCRP Breast cancer resistance protein
CHF Chronic heart failure
CL$_{int}$ Intrinsic clearance

COPD Chronic obstructive pulmonary disease
CYP Cytochrome P450
ER Extraction ratio
FcRn Neonatal Fc-receptor
GIT Gastrointestinal tract
IFN Interferon
IL Interleukin

MRP Multidrug resistance-associated protein
OATP Organic anion transporter protein
P-gp P-glycoprotein

TNF Tumor necrosis factor
UGT UDP-glucuronosyltransferase

INTRODUCTION

In today's contemporary medical arena, medical practitioners have at their disposal numerous drugs to treat acute and chronic diseases. Furthermore, many patients take multiple drugs daily to treat one or more illnesses, in particular, the increasing elderly population. This combination of events naturally leads to an increased number of drug—drug interactions. Although drug—drug interactions are becoming more predictable due to our understanding of the effect drugs can have on drug-metabolizing enzymes (expression and inhibition), our understanding of the effect of disease states on drug metabolism and disposition is less well comprehended. Many diseases are accompanied by one or more physiological and biochemical changes that affect the absorption, distribution, metabolism, and elimination (ADME) of drugs. These physiological/biochemical changes can lead to changes in the clearance, exposure, and distribution of drugs. There are often multiple changes that occur simultaneously during the course of a disease; therefore the overall effect of a disease on the pharmacokinetics of a drug can be complex. In addition, the degree of disease severity will also impact these changes, i.e., increasing severity of disease leading to increased physiological/biochemical changes.

The most significant organs related to absorption, drug metabolism, and elimination include the liver, intestine, and kidneys. Changes in the normal function of these organs due to disease will have the greatest impact on drug exposure and efficacy. For example, celiac disease and changes in drug absorption (Tran et al., 2013) or irregular drug absorption in Parkinson's disease (Nyholm and Lennernas, 2008). Liver disease has been shown to have an effect on the expression of drug-metabolizing enzymes and elimination of some drugs, as well as significant interindividual variations in drug elimination in the case of nonalcoholic fatty liver disease or cirrhosis (Merrell and Cherrington, 2011; Palatini et al., 2010). Lastly, kidney disease has been shown to have effects beyond the expected reduction in renal clearance with effects on drug-metabolizing enzymes and drug transporters in the kidney and liver (Nolin et al., 2003; Yeung et al., 2014).

In regards to drug interactions, the pharmaceutical industry has concentrated on the ability to predict and eliminate drug—drug interactions, but is less likely to incorporate the effects of various diseases on drug ADME disposition (drug—drug interactions) in the development process. This is particularly true during the drug discovery stage where the emphasis is bringing forward compounds that have appropriate potency to the target, reasonable overall ADME properties, and a satisfactory safety profile. It is not until clinical development that particular attention is given to how a drug may need to be tailored (changes in dose or dosing regimen) when administered while treating certain diseases or concomitant diseases associated with the primary disease.

This chapter begins with a survey of general drug metabolism principles, such as biotransformation reactions, major drug-metabolizing enzymes, drug absorption and elimination, and enzyme expression. For a more comprehensive review of drug metabolism principles, the reader is referred to Parkinson et al. (2013). The remainder of the chapter describes major physiological and biochemical changes that occur in various disease states and the impact they have on the ADME characteristics of drugs. These changes and their effects are illustrated throughout the chapter using pharmacokinetic principles and literature examples from animal and human studies. The majority of the chapter is devoted to drug metabolism and the effects that naturally occurring or inherited diseases can have on drug exposure. However, keeping in mind that metabolism is only one element that controls drug exposure, the remaining portion of the chapter describes how disease can affect the absorption and distribution of drugs, as well as physiological changes like blood flow, and how disease affects the expression of drug transporters.

OVERVIEW OF DRUG METABOLISM

Once administered, drugs can be eliminated from the body by one of three major pathways or routes. Polar drugs are often eliminated intact in urine via the kidneys, and both polar and nonpolar drugs can be eliminated directly through bile. Lastly, and most importantly, drugs are most often metabolized by endogenous enzymes and then eliminated in urine or bile. Drug metabolism or drug biotransformation is the process by which xenobiotics are enzymatically modified to make them more readily excretable and eliminate pharmacological activity. In most cases, this involves modifications to the parent drug or addition of functional groups that make the parent drug molecule more hydrophilic and more amenable to elimination. The liver is the major organ where drug metabolism occurs followed in significance by the intestine and kidneys and a variety of additional organs to a lesser degree (e.g., blood, skin, and brain).

Drug-metabolizing enzymes are generally categorized into two classes (phases 1 and 2) based on the type of biotransformation they perform. Phase 1 enzymes are considered oxidative or hydrolytic enzymes. They typically increase the polarity of molecules by the addition of a hydroxyl group (oxidative) or the unmasking of a more polar functionality (hydrolytic), such as the cleavage of an amide or ester bond to expose the free amine or carboxylic acid, respectively (both being more polar than the original amide or ester). Typical phase 1 oxidative enzymes include: cytochrome P450 (CYP) enzymes, flavin monoxidases, monoamine oxidases, alcohol/aldehyde oxidoreductases, and aldehyde/xanthine oxidases. Phase 1 hydrolytic enzymes include: epoxide hydrolases, esterases, and amidases. The CYP family of enzymes is by far the predominant biotransformation pathway or elimination process for the majority of marketed drugs. The second class of drug-metabolizing enzymes is called phase 2 conjugative enzymes. Phase 2 enzymes are responsible for conjugating parent drug molecules or metabolites derived from phase 1 metabolism by enzymatic addition of a polar group. Typical phase 2 enzymes and their conjugates include: UDP-glucuronosyltransferases (UGTs) that conjugate UDP-glucuronic acid, sulfotransferases that conjugate a sulfate group, glutathione S-transferases that conjugate the tripeptide glutathione, N-acyltransferases that conjugate an acetyl group to an amine, and methyltransferases (MTs) that conjugate a methyl

group. All of these reactions create larger and more polar metabolites, making them easier for the body to eliminate in bile or urine. A notable exception is the MTs, which generally make the parent drug or metabolite less water soluble (less hydrophilic); fortunately MTs constitute a minor phase 2 pathway for drugs. Of all the phase 2 pathways, the UGT family of enzymes metabolizes the greatest number of drugs and metabolites.

The systemic exposure of the drug depends on its bioavailability. Following an oral dose, the drug moves through the lumen of the gastrointestinal tract (GIT) and is absorbed by the epithelial cells. The fraction that is absorbed from the lumen (f_a) can be metabolized by the enzymes in the gut wall. The fraction that escapes gut wall metabolism (f_g) then moves through the portal vein to the liver, where it undergoes first-pass metabolism. The bioavailability of a drug is the product of the fraction absorbed (f_a), the fraction that escapes gut wall metabolism (f_g), and the fraction that escapes hepatic clearance (f_h). Fig. 1.1 describes the processes a drug goes through before it reaches the systemic circulation (drug exposure). Disease states can influence one or more of these processes ultimately influencing the bioavailability of the drug and these will be discussed throughout the chapter.
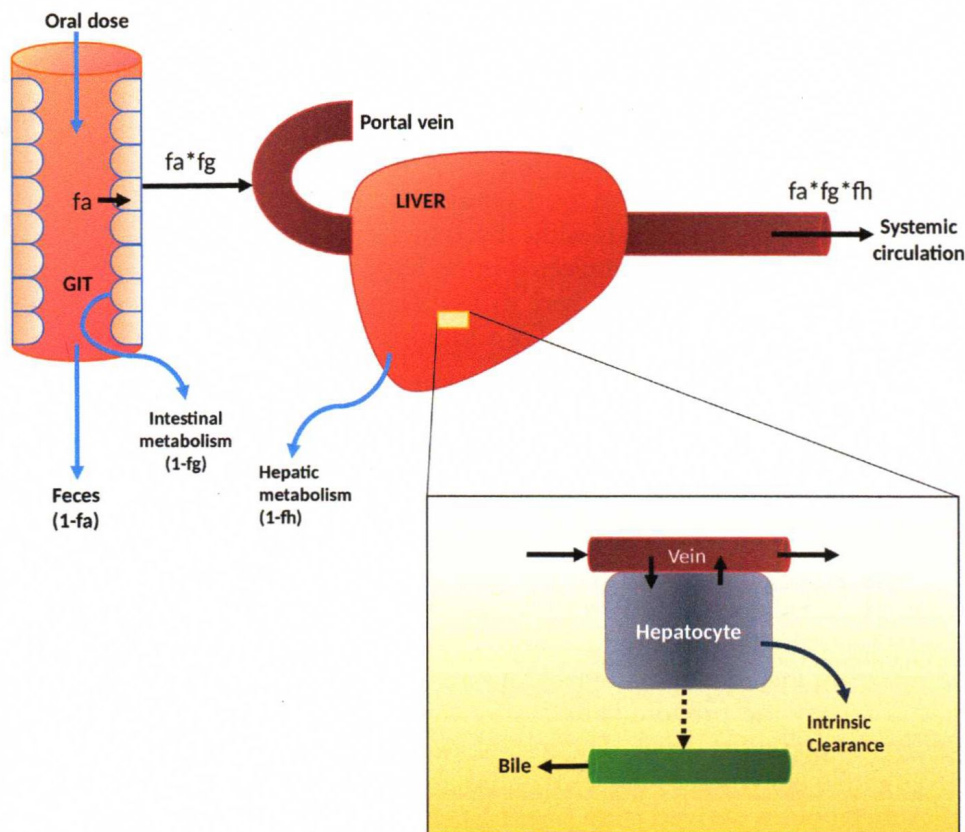

FIGURE 1.1 Overview of factors affecting oral bioavailability. Bioavailability depends on the fraction of dose absorbed (f_a), the fraction that escapes gut wall metabolism (f_g), and hepatic metabolism. The inset illustrates the route a drug may take once in the liver: from blood to hepatocyte, back to blood or into bile (either as parent drug or metabolite).

Changes to the expression (or activity) of these phase 1 and 2 enzymes, in particular the CYPs and UGTs, due to disease can have a significant impact on the rate of metabolism and systemic clearance of many drugs. Hepatic or liver clearance (CL_h) is related to liver blood flow (Q_h) and intrinsic clearance (CL_{int}) as shown in Eq. (1.1).

$$CL_h = Q_h\left(\frac{CL_{int}}{Q_h + CL_{int}}\right) \tag{1.1}$$

CL_{int} represents the ability of the liver to clear unbound drug from the blood when there is no flow limitation demonstrating the inherent enzyme activity of the drug-metabolizing enzyme. Any increase or decrease in the CL_{int} of an enzyme results in a commensurate change in the hepatic clearance of a drug that is significantly metabolized by that particular enzyme.

The regulation or expression of drug-metabolizing enzymes is controlled by two main mechanisms. The most common mechanism of enzyme expression is mediated by nuclear receptors or transcription factors, such as the aryl hydrocarbon receptor, pregnane X receptor, or constitutive androstane receptor (Xie, 2009). Combined, these three transcription factors control the normal expression of most drug-metabolizing enzymes and drug transporters. These receptors can be activated through binding of drugs to the receptor leading to an increase in the expression of drug-metabolizing enzymes (increased CL_{int} and CL_h). The second less common mechanism of enzyme regulation is stabilization of the mRNA or protein (Koop and Tierney, 1990). By decreasing the degradation of mRNA or protein (with no change in expression level), the pool of active enzyme accumulates and can be responsible for enhanced metabolism and greater elimination of drug.

Most often, diseases cause suppression of expression of drug-metabolizing enzymes (Gandhi et al., 2012; Shah and Smith, 2015). The suppression of CYPs is predominately attributed to decreases in transcription; however, it can also be due to decreased translation or posttranslational modification of CYPs (Riddick et al., 2004). This suppression leads to a reduction in enzyme expression and pool of active enzyme (decreased CL_{int} and CL_h), leading to decreases in drug elimination. Cytokines (small proteins associated with cell signaling) have been shown to suppress CYP expression and enzyme activity in human hepatocyte cultures, and the effect has been shown to be gene specific. For example, interleukin 1 (IL-1) has been shown to downregulate CYP2C8 and CYP3A4 mRNA expression by 75–95%, with no effect on CYP2C9 or CYP2C19 (Aitken and Morgan, 2007). Additional studies have shown that an increase in IL-6 concentration results in suppression of CYP3A4 in primary human hepatocytes (Dickmann et al., 2011).

DISEASE EFFECTS ON DRUG METABOLISM

Although aging is not considered a disease, studies on the liver changes that occur with age do provide insight into how diseases may affect the liver and its ability to metabolize drugs. As we age, our ability to metabolize drugs decreases; this is thought to be due to several physiological changes that occur in the liver, such as an ~40% decrease in liver volume, an ~40% decrease in liver blood flow, and a decline in the expression of CYP enzymes (Tajiri and Shimizu, 2013). Not surprisingly, acute or chronic diseases of the liver

(e.g., cirrhosis or infection) that reduce the number of viable hepatocytes, alter blood flow, or reduce enzyme levels have an effect on drug clearance and exposure (Bruha et al., 2012).

Liver Disease

Liver cirrhosis is associated with several different effects that can influence drug exposure. A common phenomenon associated with liver cirrhosis is portal-systemic shunting, a physiological change that diverts blood drained from the intestine to the systemic circulation consequently bypassing its normal route to the liver. This shunting of blood away from the liver has the effect of increasing the bioavailability of orally administered drug as they do not enter the liver to be metabolized. In addition, a lack of oxygen (oxygen is an obligatory cofactor for all CYP enzymes) could lead to decreased enzyme function (Verbeeck, 2008). It has also been shown that CYP levels (reduced activity) in patients suffering from cirrhosis change with the severity of the disease. In the early stages of the disease, CYP3A4 and CYP2C19 are affected, whereas in the later stages of the disease CYPs 1A2, 2D6, and 2E1 are also affected (Verbeeck, 2008). The effects of liver cirrhosis appear to have a greater impact on the CYP enzymes than on phase 2 enzymes, such as glucuronidation, although in severe states of cirrhosis, glucuronidation is also affected.

Hypoxia is a deficiency in the amount of oxygen reaching tissues. Hypoxia due to cardiorespiratory disease has been shown to affect the metabolism and exposure of several drugs. The elimination of theophylline (CYP1A2 substrate) and tolbutamide (CYP2C substrate) was shown to change in patients with hypoxia. The elimination of theophylline was decreased, whereas the elimination of tolbutamide was increased (du Souich and Fradette, 2011). The clearance of both drugs is blood flow independent, so the changes in elimination are likely due to changes in mRNA expression or enzyme activity of CYP1A2 and CYP2C.

Influence of Infection and Inflammation

Infection and inflammation are known to have effects on the hepatic and extrahepatic metabolism of drugs, and many chronic diseases are often associated with inflammation (Gandhi et al., 2012; Morgan, 2001, 2009; Shah and Smith, 2015). Wooles and Borzelleca (1966) demonstrated that inflammation led to a decrease in drug metabolism activity in mice. After a decade, it was shown that infection along with inflammation led to an increase in quinine exposure (due to reduced metabolism) in patients suffering from malaria (Trenholme et al., 1976). Inflammation is the result of a tissue's attempt to adapt to cellular stress by releasing inflammatory cytokines IL-1β, IL-6, tumor necrosis factor alpha (TNF-α), and interferons (IFNs) α/γ, all of which are thought to affect (suppress) the expression of CYP enzymes (Feghali and Wright, 1997).

In patients with rheumatoid arthritis, chronic inflammation results in downregulation of CYP3A4 activity. In clinical studies with tocilizumab, an anti-IL-6 antibody approved for use in rheumatoid arthritis, an increase in the CYP3A4 function was observed by way of increased clearance of simvastatin, a substrate of CYP3A4 (Schmitt et al., 2011). Infusion with the anti-IL-6 antibody results in restoring the CYP3A4 levels to normal levels, leading to a significant decrease in simvastatin exposure [fourfold decrease in the area under the curve

(AUC), 1 week post dose] and a twofold increase in simvastatin clearance. Interestingly, there was no change in the pharmacokinetics of other concomitant medication, such as omeprazole (CYP2C19 substrate) or dextromethorphan (CYP2D6 substrate) (Evers et al., 2013).

Cancer is another disease associated with inflammation and inflammation-associated cytokines. Patients with cancer often exhibit higher levels of the cytokines IL-6 and TNF-α than normal healthy individuals (Filella et al., 1996). These elevated levels of cytokines are likely to downregulate the expression and enzyme activity of CYP3A4, which will affect the pharmacokinetics of many drugs, including anticancer drugs such as docetaxel, erlotinib, and vemurafenib.

Immunotherapy is a rapidly advancing field for the treatment of cancer. Ipilimumab is an anti-CTLA-4 (cytotoxic T-lymphocyte associated protein 4) antibody that has been approved for use in advanced melanoma. Inhibition of the CTLA-4 protein results in upregulation of T-cell activity and proliferation. Nivolumab is an anti-PD1 antibody, approved for use in non–small cell lung cancer and melanoma. PD1 is an immune checkpoint that dampens the immune response to prevent damage to tissues. Production of TNF-α, IL-6, and interferon γ is increased following anti-CTLA-4 and anti-PD-1 treatment (Curran et al., 2010; Dulos et al., 2012). In addition to the inflammation already inherent to cancer, these immunomodulators also have the potential to further impair CYP-mediated metabolism (Harvey and Morgan, 2014).

A study by Dostalek et al. found that the activity and expression level of CYP3A4 in patients with diabetes mellitus are significantly reduced. Human liver microsomes isolated from diabetic livers were shown to have decreased expression and activity of CYP3A4, which corresponds with observations from animal models of diabetes (Dostalek et al., 2011; Wang et al., 2007). The downregulation of CYP3A4 was attributed to elevated levels of IL-6 and TNF-α found in diabetic patients (Morgan, 1997).

Chronic Kidney Disease

The kidney contributes to the elimination and metabolism of a wide variety of drugs; it is highly distinct from other organs of metabolism since it has specific regions of cellular activity. The CYP enzymes are found in the renal tubular epithelial cells of the renal cortex. Studies in animal models of renal failure show a decrease in protein expression and activity of CYP2C11 and CYP3A2 (Leblond et al., 2002). Rat hepatocytes treated with uremic serum from patients with advanced chronic renal failure led to a 35% reduction in the protein and mRNA expression of CYP2C6, 2C11, 3A1, and 3A2, as well as a reduction in CYP enzyme activity (Dreisbach and Lertora, 2008). As in Eq. (1.1), hepatic clearance depends on intrinsic clearance, as well as drug-free fraction [Eq. (1.4)]. A decrease in CYP expression results in a decrease in intrinsic clearance, thus increasing the bioavailability. In renal failure, along with a decrease in enzyme expression, there is also a decrease in serum albumin levels, increasing the free fraction of the drug. The relative magnitude of changes in free fraction and intrinsic clearance will determine the net effect on the bioavailability. Moreover, phase 2 drug-metabolizing enzymes are also affected in patients with kidney disease as observed by the increase in morphine exposure (due to reduced glucuronidation of morphine) in patients as compared with control subjects (Osborne et al., 1993).

Disease Effects and Genetic Disorders

Some genetic disorders can lead to physiological/biochemical changes that may have profound effects on endogenous components, as well as drugs. Crigler−Najjar syndrome and Gilbert syndrome are disorders affecting the metabolism of bilirubin. In both Gilbert syndrome and Crigler−Najjar syndrome, activity of the phase 2 enzyme UGT1A1 is diminished or absent. Therefore drugs that are substrates of UGT1A1 cannot be metabolized/eliminated and can cause potential toxicity. A good example of this is irinotecan, an anticancer prodrug that is converted to its active form SN-38, which has a narrow therapeutic index. SN-38 is mainly inactivated by UGT1A1. The lack of the UGT1A1 enzyme leads to toxicity in oncology patients treated with irinotecan (Cecchin et al., 2009). Ethinylestradiol is also a substrate for UGT1A1 (Ebner et al., 1993). Therefore women using ethinylestradiol as a component of an oral contraceptive and who have Gilbert or Crigler−Najjar syndrome are at increased risk for hyperbilirubinemia and/or estrogen-related adverse effects. Glucuronidation and the impact of these genetic disorders have been reviewed in detail by Strassburg (2010) and de Wildt et al. (1999).

DISEASE EFFECTS ON ABSORPTION PARAMETERS

Absorption of drugs takes place by passive diffusion, paracellular transport, or carrier-mediated transport. Paracellular transport (i.e., movement of compounds through fenestrations in the membrane) depends on the size of the molecule (<500 g/mole) and largely occurs with water-soluble compounds that cannot move through cells. Active transport (carrier-mediated transport) is carried out by transporters that may exist on the luminal or abluminal side of cell membranes. Additional discussion of drug transporters and disease effects are described later in the chapter.

Changes in Permeability

A major mechanism of drug absorption through the GIT as well as transport through membranes is by passive diffusion. The rate of diffusion/transport in turn depends on the concentration gradient of the solute across the membrane, the surface area available for absorption, and the permeability of the compound as described by Eq. (1.2).

$$\text{Rate of transport} = \text{Permeability} \times \text{Surface area} \times \text{Concentration gradient} \qquad (1.2)$$

The permeability of a drug depends on its intrinsic properties such as size, lipophilicity, and charge. Small, lipophilic, and unionized molecules are able to cross membranes more easily than larger hydrophilic molecules, such as peptides and proteins. Permeability also depends on the thickness of the membrane. Patients with irritable bowel syndrome typically have damaged, thinner intestinal mucosa, leading to increased gut permeability (Spiller et al., 2000). In addition to changes in permeability, delayed gastric emptying observed in patients with irritable bowel syndrome is likely to change the rate and extent of absorption of drugs.

The distribution of compounds can also be influenced by permeability into tissues. The blood−brain barrier is vital in protecting the brain from xenobiotics. The endothelial cells

in the brain capillaries have tight junctions as well as glial processes that limit the permeability of most polar drugs. In addition, a range of efflux transporters are expressed on the luminal side of brain capillaries and actively pump compounds out of the brain. Growth of certain brain tumors can cause changes in the vasculature of tumor microvessels leading to development of fenestrations in the endothelial layer (Loscher and Potschka, 2005). Preclinical tumor models have demonstrated that the permeability of certain drugs such as methotrexate is enhanced when tumors are present, allowing more drugs to reach the brain (Groothuis, 2000).

Changes in Gut and Lung Surface Area

Patients with celiac disease show atrophy of the villi in the small intestine, decreasing the surface area available for absorption. A study in patients with hypothyroidism showed that patients with celiac disease required higher doses of levothyroxine than patients without celiac disease (Tran et al., 2013). Interestingly, patients who were treated for celiac disease, who would presumably have repaired/improved small intestines over time, required lower doses of levothyroxine, supporting the hypothesis that the small intestine atrophy limited the absorption of levothyroxine.

The pulmonary route of administration is useful because absorption through the lungs can bypass first-pass metabolism in the liver. In addition, the lungs are highly vascularized and have a high surface area, allowing for efficient absorption. Several anesthetics and other drugs, such as nicotine, antibiotics, and protein therapeutics are administered via the lungs, resulting in good systemic exposure. Pulmonary disorders that result in airflow obstruction or airway inflammation due to asthma or chronic obstructive pulmonary disease (COPD) could potentially alter the extent of systemic absorption. However, in the case of inhaled corticosteroids, such as fluticasone, it has been shown that lowered systemic absorption of the steroids in patients with COPD and asthma actually reduces undesired suppression of the adrenal and pituitary glands as compared with healthy volunteers (Singh et al., 2003). In this situation, the limited systemic absorption is beneficial as it decreases drug exposure to the adrenal and pituitary glands thereby decreasing the undesired side effects.

Changes in Gastric Emptying Time

Gastric emptying and intestinal transit time determine the available time that a drug is in contact with the absorptive surfaces in the GIT. According to the pH-partition hypothesis, only unionized drugs can cross cellular membranes. Even weakly acidic drugs, more likely to be unionized in the stomach, are mostly absorbed from the small intestine due to its larger surface area. For example, for a weakly acidic drug such as paracetamol, the rate of absorption is directly related to the rate of gastric emptying; faster absorption is observed in subjects with faster gastric emptying (Prescott, 1974). On the other hand, the absorption of drugs that have slow dissolution characteristics could be enhanced by a decrease in gastric motility and increased intestinal transit time. The following examples help illustrate how these changes affect the absorption of drugs.

The treatment of Parkinson's disease depends on oral administration of the dopamine precursor levodopa. Levodopa is primarily absorbed from the small intestine; therefore gastric