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Drug Disposition in Pathophysiological Conditions

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Abstract

Expression and activity of several key drug metabolizing enzymes (DMEs) and transporters are altered in various pathophysiological conditions, leading to altered drug metabolism and disposition. This can have profound impact on the pharmacotherapy of widely used clinically relevant medications in terms of safety and efficacy by causing inter-individual variabilities in drug responses. This review article highlights altered drug disposition in inflammation and infectious diseases, and commonly encountered disorders such as cancer, obesity/diabetes, fatty liver diseases, cardiovascular diseases and rheumatoid arthritis. Many of the clinically relevant drugs have a narrow therapeutic index. Thus any changes in the disposition of these drugs may lead to reduced efficacy and increased toxicity. The implications of changes in DMEs and transporters on the pharmacokinetics/pharmacodynamics of clinically-relevant medications are also discussed. Inflammation-mediated release of pro-inflammatory cytokines and activation of toll-like receptors (TLRs) are known to play a major role in down-regulation of DMEs and transporters. Although the mechanism by which this occurs is unclear, several studies have shown that inflammation-associated cell-signaling pathway and its interaction with basal transcription factors and nuclear receptors in regulation of DMEs and transporters play a significant role in altered drug metabolism. Altered regulation of DMEs and transporters in a multitude of disease states will contribute towards future development of powerful in vitro and in vivo tools in predicting the drug response and opt for better drug design and development. The goal is to facilitate a better understanding of the mechanistic details underlying the regulation of DMEs and transporters in pathophysiological conditions.

Keywords

Inflammation; drug metabolizing enzymes; drug transporters; pharmacokinetics; Toll-like receptors; cytokines

1. INTRODUCTION

Drug metabolism can either lead to detoxification, bio-inactivation and/or elimination of drugs from the body. Metabolism can be broadly categorized into phases I and II. Phase I drug metabolizing enzymes (DMEs) primarily comprise of the Cytochrome (CYP) 450 family of enzymes. Within the 50 years after P450 discovery, tremendous research efforts on mammalian CYPs have shown that CYPs are not only involved in the biotransformation of drugs and xenobiotics but also to play a crucial role in the synthesis and metabolism of a variety of endogenous compounds such as steroids, fatty acids, prostaglandins, vitamins and bile acids. CYP3A4 is the most common isoform expressed in human liver and intestine accounting for ~30–60% of CYPs [1]. More than 50% of the currently marketed drugs are metabolized by CYP3A4 in humans [2]. Phase II metabolism consists of conjugation reactions such as glucuronidation, sulfation, glutathione conjugation or methylation forming

polar metabolites leading to enhanced excretion [3, 4]. Drug transporters play a central role in the absorption, distribution, metabolism and elimination (ADME) processes of xenobiotics across the cellular barriers. They are broadly classified into uptake and efflux transporters which facilitate drug disposition in or out of the cells [5]. Major transporters include, but are not limited to: multidrug resistant gene/P-glycoprotein (MDR/P-gp), multidrug resistance associated protein (MRP1-3), breast cancer resistance protein (BCRP), organic anion transporting peptides (OATPs) and organic cationic transporters (OCTs) [5].

Several studies have shown that drug metabolism and transport is disrupted during pathophysiological conditions primarily due to reductions in gene expression of these enzymes and transporters (Fig. 1) [6, 7]. Altered drug metabolism can lead to adverse drug reactions which account for ~10% of hospitalized cases [8]. However, due to underreporting, the actual incidences may be much higher [9]. As early as 1960s, variations in drug metabolism were reported in patients or animals with diabetes [10], cancer [11], hepatitis [12] or influenza [13] along with a corresponding change in the PD of drugs [10, 14]. These early studies prompted researchers to further elucidate DME and transporter gene expression and PK/PD of clinically-relevant drugs in pathophysiological conditions such as obesity, rheumatoid arthritis, non-alcoholic fatty liver disease (NAFLD) and cardiovascular diseases (CVDs) such as hypertension, heart failure, or stroke. The possible mechanistic pathways regulating the DMEs and transporters during these pathophysiological conditions are discussed.

Cell-signaling components including the transcription factors such as nuclear factor-κB (NF-κB) or CAAT enhancer-binding protein (C/EBP) [15, 16] and the xenobiotic nuclear receptors, pregnane X receptor (PXR) and constitutive androstane receptor (CAR), upon heterodimerization with the central nuclear receptor, retinoid X receptor (RXR)-α, regulate the gene expression of DMEs and transporters [17]. The orphan nuclear receptor, hepatocyte nuclear factor (HNF) 4α regulate the gene expression of PXR and CAR mediated xenobiotic induction of CYP3A4 [18]. The readers of this review will gain detailed understanding of hypothesis-driven mechanisms known to play a major role in altering the DMEs and transporters, and PK/PD (pharmacokinetics/pharmacodynamics) of clinically relevant medications in the above listed pathophysiological conditions.

2. INFECTION AND INFLAMMATION

2.1. Bacterial infections

2.1.1. Drug metabolizing enzymes—Most of the studies on regulation of DMEs have been documented with gram-negative bacteria. Clinically relevant cecal ligation and puncture (CLP) or inflammatory bowel disease (IBD) induced by *Citrobacter rodentium* (gram-negative pathogen) are the most frequently used models owing to their close resemblances in the progression and characteristics of human sepsis [19, 20]. Alterations in total hepatic microsomal CYP content and activities were reported in CLP rat or IBD mouse models [21, 22]. The rapid down-regulation of CYP2Cs and CYP3As after intraperitoneal (i.p) injection and CYP4As after oral injection of *C. rodentium* was quantitatively and qualitatively different, suggesting that the effects of oral infection are not due to bacterial translocation to the liver [22]. Infection of pigs with the gram-negative respiratory pathogen, *Actinobacillus pleuropneumoniae*, led to decreased microsomal metabolism of several CYP-dependent substrates 24 h after inoculation [23]. Similarly, gram-positive bacterial infections account for more than 50% of the total community acquired infections [24]. Listeriosis, caused by *Listeria monocytogenes*, is one of the most critical food-borne diseases in humans. *L. monocytogenes* induced CNS infection in rodents significantly down-regulated mRNA, protein and activity of hepatic CYPs [25].

The gram-negative and gram-positive bacterial components, lipopolysaccharide (LPS), and lipoteichoic acid (LTA), serve as sterile infection models by inducing inflammatory responses in animals [26, 27]. LPS injections down-regulate expression and activity of key hepatic, intestinal and renal DMEs in several animal species such as mice, rats or rabbits [28, 29]. The effect of LPS on CYP expression and activity is dependent on the route of administration at same dose of LPS [30]. We recently showed that LTA significantly down-regulated the gene expression of several phase I and phase II DMEs in mice [31].

2.1.2. Transporters—Changes in expression of drug transporters can have significant impact on the safety and efficacy of the drugs. LPS treatment of mice significantly down-regulated P-gp and Mrp2, major transporters involved in disposition of clinically relevant drugs such as colchicine, verapamil, daunorubicin, cyclosporin A and the abundant food-derived carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) [32, 33]. LPS-treated mice had significantly lower hepatic P-gp (30% of control) and increased P-gp expression in the kidney (140% controls) [34, 35].

2.1.3. PK/PD studies—As early as 1980's, reduced clearances of clinically relevant drugs have been reported in humans infected with BCG vaccine, *Streptococcus pneumoniae* or *Mycoplasma pulmonis* [36–38]. LPS injections in animals and humans altered PK parameters such as maximum plasma concentration (C_{max}, increase), area under the curve (AUC, increase), half-life ($T_{1/2}$), volume of distribution (V_d) and clearance (CL, deccrease) of various drugs including cisplatin, antipyrine, theophylline, hexobarbital, gentamicin and vancomycin [39–42]. Humans infected with gram-positive bacteria such as *Pseudomonas* or *Staphylococcus*, led to an increase in V_d and dilution of antimicrobial agents in plasma and extracellular fluids, requiring careful monitoring of the dosage regimen [43]. PD changes were observed in turpentine oil-injected mice which showed high anti-tumor activity of gimatecan compared to the controls [44]. On the other hand, despite of very high plasma concentrations of the calcium channel blocker, verapmil, or potassium channel antagonists, sotalol or propranolol; no change in the PD was observed in inflamed animals [45, 46]. This discrepancy may be related to altered receptor-functioning or receptor-ligand binding in inflammation. Nevertheless, the above studies need further evaluations to delineate the disparities in altered drug metabolism caused by different bacterial infections or inflammation which has significant clinical implications for drug therapy in disease states.

2.2. Viral infections

2.2.1. Drug metabolizing enzymes—Viral infections result in the release of various inflammatory mediators from the immune cells [47]. Several studies have shown deleterious effects of viral infections such as mouse-adapted influenza virus [48], Newcastle disease virus [49], encephalomyocarditis virus [50], chronic active hepatitis and cirrhosis [51, 52] and HIV infection [53] on alteration of expression and activity of DMEs and oxidative pathways in animals and humans. Decreased levels of hepatic CYP1A2 were detected in children suffering from upper respiratory tract viral infections during an influenza outbreak [13]. With exceptions of CYP2D6 mRNA and CYP1A2 activity, other major CYPs such as CYP2C9, 2C19, and 3A4 in hepatitis C virus (HCV) infected PXB mice (mouse model with human hepatocytes) were comparable to the non-infected controls [54]. Recombinant adenovirus injections in Sprague-Dawley rats led to a significant down-regulation of renal CYP2E1 and hepatic CYP3A2 and CYP2C11 expression and activity, and induction of CYP4A protein expression [55, 56].

2.2.2. Drug transporters—A recent study showed that HIV-type 1 viral envelope glycoprotein gp120 decreased P-gp and Mrp expression levels in rat astrocytes [57]. However, due to the fact that HIV infected patients are on highly active antiretroviral

therapy (HAART) consisting of numerous drugs, both, induction and suppression of drug transporters in HIV infection are reported [58]. Polyinosinic/polycytidylic acid [poly (I:C)] is widely as a model of *in vivo* viral-induced inflammation. Poly (I:C) can induce interferons (IFNs) and pro-inflammatory cytokines such as interleukin (IL)-6, IL-10, IL-12, and tumor necrosis factor (TNF)-α. A significant down-regulation of key maternal hepatic and placental drug transporters and their endogenous substrates was observed upon i.p injection of poly (I:C) in pregnant rats [59]. However, Abcb1b (ATP-binding cassette sub-family B member 1) and Abcc3 (ATP-binding cassette subfamily C) were significantly induced. A recent study in PXB mice infected with HCV reported significantly higher expression of MRP4 and OATP2B1 and lower expression of OCT1 compared to non-infected mice [54].

2.2.3. PK/PD Studies—During the 1982 influenza B outbreak in King County, Washington, 11 children whose asthma had previously been controlled with a stable theophylline dose, developed theophylline toxicity at this same dose [13]. These children had a significant decrease in CL and increase in $T_{1/2}$ of theophylline. HIV infections could also lead to altered PK of levofloxacin and fluconazole [60, 61]. End-stage liver disease, which is largely the result of HCV infection, now accounts for up to 50% of deaths among persons with HIV-1 infection [62]. A clinical study in HIV-HCV-coinfected patients showed significantly lower nelfinavir oral clearances in HIV+ and HCV+ patients with and without cirrhosis compared to HIV+ and HCV-negative patients [63]. This presses the need for therapeutic drug monitoring in individualizing nelfinavir dosage in HIV-HCV-coinfected patients. In addition, an increase in AUC and C_{max} of several anti-retrovirals are reported in HCV-infected patients with moderate liver impairment [64, 65]. Other studies also showed significantly higher AUC of docetaxel and reduced glomerular filtration rate, suggesting changes in renal CYP in rats injected with the recombinant adenovirus expressing β-galactosidase [56, 66].

2.3. Mechanisms for altered drug metabolism in infections and inflammation

Bacterial or viral infections lead to activation of Toll-like receptor (TLR) signaling pathway, which leads to the induction of pro-inflammatory cytokines, IL-1β, IL-6 and TNF-α in the immune cells. In the liver, TLRs are present on the cell surface of various immune cells (the resident macrophages or Kupffer cells) as well as the hepatocytes [67]. Out of the 13 TLRs identified in mammals, TLR4 is activated by the gram-negative component, LPS, and TLR2 is activated by the gram-positive component, LTA [68, 69]. We and others have shown down-regulation of Cyp3a11 and P-gp in LPS-sensitive TLR4 *wild type* (C3HeB/FeJ) mice could not be detected in TLR4-mutant (C3H/HeJ) mice [29]. Recent data from our group showed that down-regulation of gene expression of key hepatic phase I and phase II DMEs in $TLR2^{+/+}$ mice by LTA was blocked in $TLR2^{-/-}$ mice [31]. We also observed that LTA down-regulated Mrp2, had no effect on Mrp3 and induced Mdr1b expression. Although, most of the studies have cited the role of Kupffer cell-derived TLRs in hepatic drug metabolism, we and others have also shown that LPS or LTA treatment of primary mouse hepatocytes can directly affect the DMEs via TLRs present on the hepatocytes, independent of cytokines [70, 71]. TLR-mediated signaling is initiated by the down-stream adaptor protein, Toll-interleukin 1 receptor domain containing adaptor protein (TIRAP) [72]. We showed that TIRAP was involved only in TLR2-mediated regulation of DME and transporter genes [71], and not by TLR4 [29].

Cytokines are involved in alteration of DMEs and transporters *in vitro* [73, 74]. LPS-treatment of primary rat cocultures of hepatocytes and Kupffer cells significantly suppressed phenobarbital-mediated induction of CYP2B1 [75]. This decrease was associated with a 5-fold induction in TNF-α released from the Kupffer cells in cocultures. *In vitro* studies with cytokine-treated rat or human hepatocytes led to decreased expression and activity of several

drug transporters including efflux pumps such as P-gp, MRP2, 3 and 4, and BCRP, and uptake transporters such as OATP-B, OATP-C, and OATP-8 [76–78].

However, recent evidence suggests cytokines may not be playing a major role in regulation of DMEs. Earlier studies in TNF-$\alpha^{-/-}$ and IL-$6^{-/-}$ knockout mice revealed that DMEs were still down-regulated [79, 80]. A recent study by *Kinloch et al* in $TNFR1^{-/-}$, $IL1R1^{-/-}$ and Kupffer cell-depleted mice showed that only TNF-α, but not IL-1β or Kupffer cells, was involved in regulation of CYP3A11 and 3A25 in oral *C. rodentium* infected mice [81]. In addition, we showed that although down-regulation of DMEs was blocked in LTA-treated $TIRAP^{-/-}$ mice, hepatic cytokine gene expression remained unchanged [71].

Nitric oxide (NO), released from macrophages and hepatocytes during inflammation is also known to regulate DMEs [82]. However, contrasting results have been reported for the role of NO in regulation of DMEs in cytokine-treated primary rat hepatocytes [83, 84]. IL-1β and TNF-α-mediated down-regulation of CYP protein was NO dependent, but not in IL-6 mediated down-regulation [83]. NO was also shown to regulate the suppression of UGT activities in cytokine-treated hepatocytes [85].

Inflammation-mediated activation of NF-κB plays a significant role in down-regulation of DMEs [86, 87]. NF-κB can either indirectly regulate CYP gene expression through mutual repression between NF-κB and nuclear receptors, or can directly regulate CYP gene expression through binding to NF-κB response element in the promoter region of CYP genes [88]. Interaction of NF-κB with nuclear receptors during pathophysiological conditions can alter expression of DMEs [89]. Inflammation activates the mitogen activated protein kinase (MAPK), c-Jun-N-terminal kinase (JNK) which also regulates nuclear receptors and DMEs [90, 91]. Recent experiments in human gastric carcinoma and pancreatic carcinoma cell lines suggested a prominent role of JNK activation in down-regulation of P-gp protein expression [92]. However, further detailed studies using *in vitro* models such as cell lines or primary hepatocytes, and specific inhibitors of these cell signaling components will significantly contribute in understanding the mechanistic regulation of DMEs and transporters during inflammation.

It is known that down-regulation of DMEs and transporters during inflammation are associated with reduced expression of the regulatory nuclear receptors [29, 31, 93, 94]. We showed that down-regulation of nuclear receptors by LPS in $TLR4^{+/+}$ or by LTA in $TLR2^{+/+}$ mice was blocked in TLR4 mutant or $TLR2^{-/-}$ mice [29, 31, 71]. However, mRNA and protein expression of several CYPs did not differ in $PXR^{-/-}$ or $PPAR^{-/-}$ mice treated with LPS [95]. Similarly, it was shown that PXR was least important in regulating several efflux and uptake drug transporters using PXR *wild type* or PXR *null* mice treated with LPS [96]. However, the down-regulation of Bsep (bile salt export pump) and Mrp2 mRNA in IL6-treated *wild type* mice was attenuated in the PXR *null* mice. Thus, involvement of nuclear receptors in inflammation-mediated regulation of DMEs and transporters may depend on the nature of the inflammatory stimuli.

3. CANCER

3.1. Drug metabolizing enzymes

Owing to the fact that, most anticancer drugs have a very low or narrow therapeutic index, alteration of DMEs can lead to life-threatening adverse drug reactions or increased risk of treatment failure in patients undergoing chemotherapy. Decreased hepatic microsomal DME activity was detected in tumor bearing rats with Walker carcinosarcoma 256, where impaired metabolism of hexobarbital, strychnine and meprobamate was observed [11].

Due to difficulties in obtaining human liver tissue from cancer patients, an Engelbreth-Holm-Swarm (EHS) sarcoma mouse model bearing transgenic CYP3A4/lacZ gene was developed [97]. Reduced hepatic levels of the transgene-derived β-galactosidase, as quantified by o-nitrophenyl-β-D-galactopyranoside assay, and *Cyp3a11* mRNA and protein was observed in these mice [97]. Tumors derived from the surface of the ovary account for the vast majority of ovarian tumors (approximately 80%). Altered gene expression ratio of CYP3A4/ABCB1 (P-gp) in cancer cells grown from epithelial ovarian tumors had significant contribution in altering docetaxel disposition [98]. On the other hand, there was no significant correlation in CYP2C8/ABCB1 ratio suggesting that paclitaxel disposition may require additional critical gene products. The expression of several phase II DMEs was also characterized in EHS tumor-bearing mice [97]. Out of 8 GSTs studied, six were reduced and two unchanged; SULT1A1 was increased while SULT2A1 and UGT2B5 were reduced, and no change was observed in UGT1A7. Tamoxifen remains the first-line targeted treatment for the estrogen receptor α-positive breast cancer patients and undergoes metabolism in the breast tissue which also consists of several DMEs [99]. In a study examining the role of methylation patterns of genes responsible for tamoxifen metabolism, higher methylation rate of N-acetyl transferase-1 (NAT1), a phase II DME gene, was observed in human breast cancer tissues compared to control breast tissues [100].

3.2. Drug transporters

Changes in the genetic variability in clinical specimens as well as over expression of ABC transporter family in tumors have been shown to play a critical role in multidrug resistance to several anticancer drugs [101–103]. A recent study showed significant reductions in the mRNA levels of Mdr2, Mrp2, Mrp3, Ntcp, Oatp 2, Bsep, Bcrp, whereas Mdr1a and Oatp1 remained unchanged [104].

3.3. PK/PD studies

Cancer-induced changes in the PK and PD profiles of several drugs have been documented since the late 1960s [14, 105]. In a clinical study, the absorption rate constant, apparent V_d and serum CL of penbutolol (antihypertensive drug) were significantly reduced in the cancer group [106]. PD effect (reduction in heart rate) of penbutolol did not vary statistically in respect to baseline values in cancer patients [106]. Reduction in the metabolism of omeprazole (CYP2C19 substrate) has also been observed in patients with advanced cancer [107]. Reduced CYP3A expression resulted in >2 fold increase in the sleep time in tumor bearing mice receiving the widely used sedative-hypnotic, midazolam (CYP3A specific substrate) [97].

3.4. Mechanisms of cancer-mediated altered drug metabolism

Since the 1800s, it was observed that chronic inflammation is frequently associated with the onset and progression of various cancers [108]. A strong association between cancer progression and induction of cytokines or acute phase reactive proteins in tumors is documented [109, 110]. For e.g. EHS tumor-bearing mice had significantly higher circulating plasma levels of IL-6 (25 pg/ml) compared to the control mice (below detection limit). IL-6 mediated activation of JNK was also evident in EHS tumor-bearing mice, which again prompts the important role of JNK in regulation of DMEs. Studies have shown that TLR expression is enhanced in tumor cells lines [111]. However, the role of TLRs in alteration of DMEs and transporters in cancer has never been investigated.

The role of NF-κB activation in acute inflammation has been suggested in carcinogenesis [112, 113]. Cancer-mediated alteration of DMEs and transporters may possibly be regulated by over-expression of NF-κB. A recent study highlighted the role of extra hepatic malignancies in down-regulation of PXR and CAR in tumor-bearing mice [114]. This study

prompts to link the reduction in nuclear receptors with altered drug metabolism in cancer. However, additional studies with nuclear receptor knockout animal models with tumors will help identify their direct role in regulation of DMEs and transporters. Overall, all these studies imply that tumor-mediated inflammation may play an integral role in drug response and toxicity of various anticancer agents.

4. DIABETES AND OBESITY

4.1. Drug metabolizing enzymes

Another prevalent pathophysiological condition affecting millions of people in the world is the occurrence of diabetes and obesity. As per the latest statistical report, 366 million people in the world will have diabetes by 2030 [115]. *Dixon et al* demonstrated that alloxan-induced diabetes decreased hexobarbital, chlorpromazine, and codeine metabolism in male rats [10, 116]. Although, streptozotocin-induced diabetes in rats and hamsters significantly induced hepatic and renal CYP2E1 and 4A2 protein levels [117, 118], suggesting altered metabolism of ketones and fatty acids in diabetes, hepatic CYP2E1 protein levels remained unchanged in streptozotocin-induced diabetic mice livers [118, 119]. A recent study showed differential effects of alloxan-induced diabetes on protein expression and activity of CYP2E1 (increased) and CYP2B4 (decreased) in rabbits [120]. Altered gene expression of DMEs in genetically obese zucker fatty rats (reduction in CYP2B1/2 and Mrp3) and *db*/*db* mice (increase in CYP2B10) are also reported [121, 122]. Studies have reported interesting results on DME gene and protein expression for different diet-induced obese (DIO) animal models. E.g. Although Cyp3a11 gene and protein expression were significantly reduced in both long term (12 weeks) and short term treatment (1 week) of high fat diet (HFD), Cyp2c9 gene expression was significantly reduced only in the short term HFD treatment [123]. On the other hand, gold thioglucose induced obese mice had significant elevations in CYP2B10 and CYP4A10 gene expression [123]. We recently showed that mRNA levels of the phase II DMEs (Ugt1a1, Sult1a1, Sultn) were reduced ~30–60% in mice fed high-fat diet (HFD, 60% kcal fat for 14 weeks) compared to low fat diet (LFD, 10% kcal fat) mice [124]. RNA levels of Cyp2e1 and Cyp1a2 were unaltered in HFD mice. These findings indicate that regulation of CYPs is dependent on the model of diabetes and obesity, and is tissue, isoform and species-specific.

4.2. Drug transporters

Streptozotocin treatment in rats increased hepatic levels of *Mdr*2, leading to increased phospholipid secretion into bile [125]. Another study also showed that the hepatic expression of uptake transporters (Oatp1a1, 1a4, 1b2, 1a6, 2b1, and Ntcp) in diabetic mice decreased significantly compared to the *wild type* controls [126]. Our recent study showed no effect of high fat in DIO mice on gene expression of hepatic transporters (Mrp2 and 3, and Mdr1b) [124].

4.3. PK/PD studies

Obesity-associated alterations in phase II metabolism were reported in 1980's. For e.g. clearances of oxazepam and lorazepam, widely used benzodiazepines and excreted as glucuronide conjugates, were significantly increased in obese patients [127]. Similarly, increased metabolism of chlorzoxazone (CYP2E1 substrate) to 6-hydroxychlorzoxazone was observed in obese individuals. This was attributed to increased CYP2E1 activity associated with obesity [128]. Animal studies performed using a diabetes mellitus rat model (induced by alloxan or streptozotocin treatment) have reported altered PK of drugs such as acetaminophen (APAP), chlorzoxazone, furosemide, and methotrexate [129–132]. A recent clinical study demonstrated accelerated clearance and a decrease in the AUC of levofloxacin in ambulatory obese individuals compared to the normal weight [133]. Although, no

changes in PD of atracurium were reported in obese animals compared to lean control [134], triazolam-induced sedation in obese patients increased significantly compared to normal weight men [135]. We also observed similar disparities in the PD of midazolam, CYP3A substrate, (increased sleep time) and zoxazolamine, CYP2E1 substrate (no change) in DIO mice [124]. This can be attributed to decrease in CYP3A and no change in CYP2E1 expression. Thus, the differential effects of obesity on PD of drugs may depend on the DME, the drug or the target organ itself.

4.4. Mechanisms of altered drug metabolism in diabetes/obesity

The major pathophysiological manifestation in diabetes/obesity is characterized by low-level chronic and local inflammation, such as release or over expression of TNF-α and C-reactive protein in adipose tissue [136, 137]. However, the role of inflammation in regulation of DMEs and transporters in diabetes/obesity remains unclear. Hormonal regulation of DMEs in diabetes/obesity has also been addressed before [138]. Although an increase in mRNA or protein levels of CYP2E1 have been observed in obese patients [139], *db/db* mice showed no such effects [122]. This can possibly be due to hyperinsulinemia leading to a faster turnover (shorter CYP2E1 mRNA half-life) by insulin [140]. Various studies have shown that phosphatidylinositol-3-kinase (PI3K) signaling, using PI3K inhibitors, wortmannin and LY294002, ameliorated insulin-mediated decrease in CYP2E1 and phase II enzymes (α-GST) mRNA [141, 142].

Interestingly, lower expression of CAR and CYP2B in obese Zucker rats and ~2 fold induction in obese and genetically diabetic mice (*db/db*) on HFD [121, 123] were reported. This discrepancy in obese Zucker rats and *db/db* mice in regulating expression profiles of CYPs and nuclear receptors can be explained by the difference in the position of mutation of leptin receptor gene [143, 144]. We recently showed that expression of PXR and CAR; and protein levels of RXRα were significantly reduced in HFD mice [124]. Thus, a complex set of processes including but not limited to cytokines, nuclear receptors, insulin sensitization or downstream signaling molecules, may regulate DMEs and transporters in diabetes/obesity.

5. NON-ALCOHOLIC FATTY LIVER DISEASE

5.1. Drug metabolizing enzymes

Non-alcoholic fatty liver disease (NAFLD) is highly prevalent with an estimated world population between 14% and 24% being affected. NAFLD comprises of symptoms ranging from simple steatosis (fatty liver) to the more severe non-alcoholic steatohepatitis (NASH, fatty liver with infiltration of inflammatory cells) to progressive hepatic fibrosis and to cirrhosis [145]. Alteration of hepatic CYP2E1 was first noted in humans with NASH [146]. Later studies have shown significant contribution of NAFLD (comprising of both, simple stage fatty liver as well as NASH) on expression and activity of DMEs in animals [147–149]. Similarly, *in vitro* studies in primary human or animal hepatocyte cell cultures from steatotic or non-steatotic livers showed a profound impact of steatosis on the metabolic functionality of hepatocytes [150, 151]. Significant reductions in CYP1A2, 2C9, 2E1 and 3A4 activities in fat-overloaded hepatocytes were observed compared with control hepatocytes prepared from the same liver [147].

5.2. Drug transporters

Decreased mRNA and protein expression of uptake transporters such as NTCP, OATP1a1, 1a4, 1b2 and 2b1; and OAT 2 and 3 were observed in NAFLD [148].

5.3. PK/PD studies

Studies have shown interesting results with APAP PK in rats and humans with NAFLD. Children with NAFLD had significantly higher concentrations of APAP-glucuronide (APAP-G) in serum and urine compared with controls, with no significant differences in PK of APAP among the 2 groups [152]. Another study showed that biliary concentrations of APAP-sulfate (APAP-S), APAP-G, and APAP-glutathione were reduced in MCD (methionine- and choline-deficient) rats [153]. However, plasma levels of APAP-G were also elevated in MCD rats, similar to that observed in children [152]. A clinical study evaluated the effect of NAFLD on PK of silymarin [154]. The $AUC_{0\text{-}24h}$ for the sum of total silymarin flavonolignans was ~3–4 fold higher in patients with NAFLD ($p<0.03$), compared with healthy volunteers.

5.4. Mechanisms of altered drug metabolism in NAFLD

Several mechanisms have been proposed for the effect of NAFLD on altered drug metabolism. Deposition of fat in human hepatocytes can lead to a marked impairment in CYP mRNA and activity [155]. *Fisher et al* observed intense staining for IL-1β in steatotic livers, indicating that experimental steatosis and NASH results in increased hepatocellular inflammation [148]. Studies have shown ambiguous results on expression of nuclear receptors and transcription factors in NAFLD [149, 156, 157]. Except for PXR, which was significantly increased by 1.4 fold, the other nuclear receptors (AhR, CAR, PPARα and Nrf2) were not altered [147]. Therefore, various factors need to be taken into account for improved pharmacotherapy in patients with NAFLD.

6. CARDIOVASCULAR DISORDERS

6.1. Drug metabolizing enzymes

CYPs in humans are responsible for metabolizing a large number of cardiovascular medications, including β-blockers, calcium channel blockers and angiotensin receptor antagonists [158]. Alteration in DMEs could be of particular clinical relevance in patients with heart failure because these patients take more than 10 medications on average. Although, not detected in the normal human heart, failing hearts expressed CYP11B1 and 11B2 [159]. Surprisingly, an up-regulation in CYP2J2, 1B1, 2E1, 4A10 and 2F2 gene expression was reported in the failing heart [160]. Increased cardiac CYP11B2 mRNA was associated with increased myocardial fibrosis and the severity of left ventricular dysfunction in patients with heart failure [161]. It was shown that the production of testosterone metabolites, including dihydrotestosterone and androstenedione, was significantly increased in hypertrophic human hearts [162]. Transient ischemic attacks (TIA) are risk factors for strokes. A recent study showed that cerebral infarct size was reduced in TIA-preconditioned animals and CYP2C11 mRNA and protein were coincidentally increased in the brain after experimentally induced TIA [163]. Genetic polymorphisms of DMEs are commonly associated with heart failure and hypertension [164]. For e.g. a study in Japanese subjects reported that CYP2C9 *wild type* carriers had lower systolic blood pressure after losartan (metabolizes to the active metabolite EXP3174) therapy than poor metabolizers [165].

6.2. Drug transporters

A recent study demonstrated a selective disease-dependent regulation of the high-affinity carnitine transporter, OCTN2, in patients with dilated cardiomyopathy, whereas the other OCT(N)s were unaffected [166].

6.3. PK/PD studies

It was shown that lidocaine plasma clearance was significantly decreased in patients with cardiac failure and this was associated with decreased liver blood flow [167]. Another group also observed reduced plasma clearance of lignocaine in patients suffering from myocardial infarction without cardiac failure [168]. Thus, the mounting evidence for the effect of CVDs on DMEs and transporters needs to be extended for further PK/PD studies. Although antihistamines exert cardiovascular effects, the effect of chronic heart failure on PK of antihistamines yet remains to be investigated.

6.4. Mechanisms of altered drug metabolism in CVDs

Failing or hypertensive hearts are susceptible to infiltration by pro-inflammatory cytokines and reactive oxygen species induced by stress [169]. Studies have shown that increased circulating levels of TNF-α and IL-6 in patients with congestive heart failure were inversely proportional to CYP2C19 and CYP1A2 activity [170]. Similarly, down-regulation of OCTN2 expression in patients with dilated cardiomyopathy inversely correlated with cardiac $CD3^+$ T-cell count [166]. In addition, cardiac cytokine release may affect OCTN2 expression during cardiomyopathy associated with inflammation.

7. RHEUMATOID ARTHRITIS (RA)

7.1. Drug metabolizing enzymes

Rheumatic diseases are estimated to affect up to 1.1% of the world's population [171]. Various studies have shown that gene expressions of DMEs are altered in adjuvant arthritis (AA) rats [172, 173].

7.2. Drug transporters

Decreased activity of hepatic P-gp in the isolated perfused liver of AA rats was reported [174, 175]. Decrease in P-gp activity corresponded with the decreased levels of Mdr1a mRNA and P-gp protein in AA rats.

7.3. PK/PD studies

PK/PD changes such as elevated plasma levels of propranolol and prolongation of sleep time with pentobarbital were observed in AA rats compared to normal rats [176, 177]. Based on these early observations, recent studies have also shown altered PK of methotrexate, T-5557 (novel anti-inflammatory agent) and doxorubicin in AA animals [174, 178]. Although, a significant increase in the plasma concentrations of verapamil in rats and humans with underlying arthritis were reported, there were no changes in the PD of verapamil (prolongation of PR interval) [45, 179]. This discrepancy was then attributed to a decrease in the receptor-ligand affinity in inflammation [180, 181].

7.4. Mechanisms of altered drug metabolism in RA

AA animal models represent a systemic inflammatory disease with bone and cartilage changes similar to those observed in RA [182]. Down-regulation of hepatic P-gp in AA rats was attributed to elevated levels of cytokines such as TNF-α and IL-6 but not IL-1β [183]. Similarly, increased plasma concentrations of drugs in AA rats correlated with increased serum TNF-α level [179]. Several *in vitro* and *in vivo* studies have shown up-regulation of NF-κB in RA and osteoarthritis [184, 185]. It was recently demonstrated that PXR and CAR expression in small intestine was decreased in arthritis [186]. Significantly decreased bilirubin elimination in collagen-induced arthritis (CIA) rats compared to normal rats [187] was attributed to decreased expression of CAR in CIA rats. Overall these studies imply an involvement of inflammatory pathways in regulation of DMEs and transporters in arthritis.

8. CONCLUSION

A common theme of this chapter is that a multiplex of mechanisms are responsible for alterations of DMEs, transporters and PK/PD of drugs in different pathophysiological conditions. It is well-established that changes in gene expression of enzymes and transporters can lead to disruption in drug disposition in altered pathophysiological conditions including infection/inflammation, cancer, obesity, CVD, rheumatoid arthritis, etc. Studies show that induction of inflammatory mediators is an underlying factor common to all these pathophysiological conditions and may contribute to altered drug disposition in disease states. In addition, the generally accepted role of cytokines in alterations of DMEs and transporters needs further evaluation. We have established the involvement of Toll-like receptor signaling pathway in the regulation of DMEs and transporters, and our studies point to the role of cytokine-independent pathways in the liver. The role of transcription factors and nuclear receptors in the regulation of DMEs and transporters in disease states need further investigation, implying an urgent need to develop models for delineating the roles of individual inflammatory mediators or nuclear receptors in altered drug disposition in disease states. It is of utmost importance to study clinically relevant drugs with known adverse effects to determine if changes in metabolism lead to increased toxicity or reduced efficacy in some individuals with underlying illness in predicting and preventing undesirable sub-therapeutic effects.

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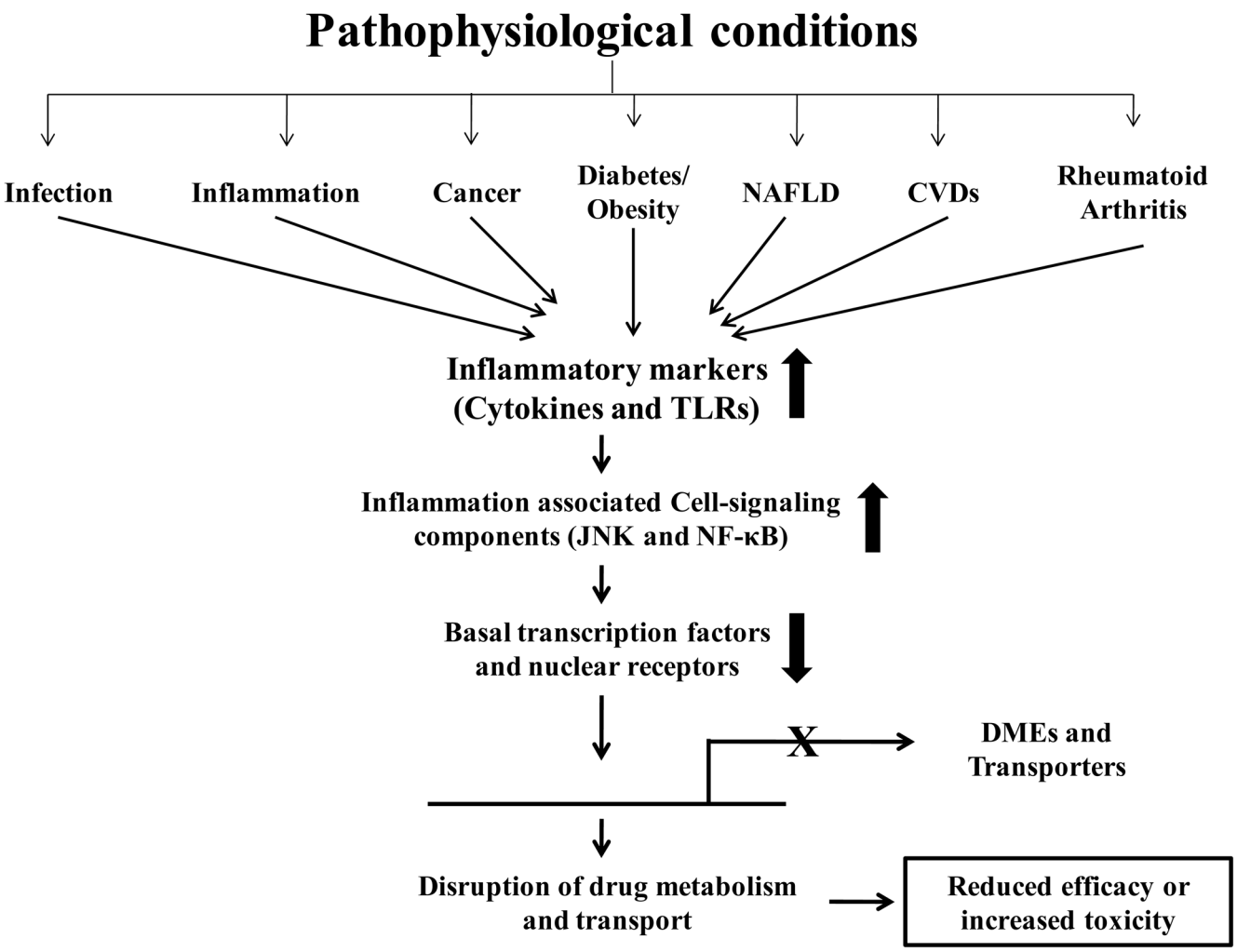

Fig. 1.
Schematic of regulation of drug disposition in pathophysiological conditions