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Drug metabolism alterations in nonalcoholic fatty liver disease

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Abstract

Drug-metabolizing enzymes play a vital role in the elimination of the majority of therapeutic drugs. The major organ involved in drug metabolism is the liver. Chronic liver diseases have been identified as a potential source of significant interindividual variation in metabolism. Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the United States, affecting between 60 and 90 million Americans, yet the vast majority of NAFLD patients are undiagnosed. NAFLD encompasses a spectrum of pathologies, ranging from steatosis to nonalcoholic steatohepatitis and fibrosis. Numerous animal studies have investigated the effects of NAFLD on hepatic gene expression, observing significant alterations in mRNA, protein, and activity levels. Information on the effects of NAFLD in human patients is limited, though several significant investigations have recently been published. Significant alterations in the activity of drug-metabolizing enzymes may affect the clearance of therapeutic drugs, with the potential to result in adverse drug reactions. With the enormous prevalence of NAFLD, it is conceivable that every drug currently on the market is being given to patients with NAFLD. The current review is intended to present the results from both animal models and human patients, summarizing the observed alterations in the expression and activity of the phase I and II drug-metabolizing enzymes.

Keywords

Nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; cytochrome p450; glutathione *S*-transferase

Nonalcoholic fatty liver disease (NAFLD)

NAFLD describes a spectrum of hepatic pathologies linked by the intracellular hepatic accumulation of fat (i.e., steatosis) in the absence of substantial alcoholic intake. NAFLD has only recently been recognized as a serious clinical disorder, and knowledge of the effect of the disease on hepatic drug metabolism is limited. This review of the literature summarizes the effects of NAFLD on the activity and expression of both phase I and II drug-metabolizing enzymes (DMEs) in various animal models of NAFLD and in patients with NAFLD. Additionally, potential mechanisms for these alterations are proposed.

Prevalence

The term NAFLD encompasses the progression from steatosis to nonalcoholic steatohepatitis (NASH), progressive fibrosis and cirrhosis, and even hepatocellular carcinoma. Although initially described 30 years ago (Adler and Schaffner, 1979; Ludwig et al., 1980), the true scope of the disease has only recently been understood. NAFLD is the

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most prevalent chronic liver disease in both the United States and many other industrialized nations (Wieckowska and Feldstein, 2008). NAFLD has been described as the hepatic manifestation of the metabolic syndrome and is often linked with obesity and insulin resistance (IR) (Reynaert et al., 2005).

The prevalence of these three conditions (NAFLD, IR, and obesity) has increased dramatically in the last few decades. In 2008, the prevalence of obese adults (body mass index [BMI] >30kg/m^2) in the United States was approximately 32% (Flegal et al., 2010), a statistic that has doubled over the last two decades. This prevalence is projected to reach more than 50% by 2030 (Wang et al., 2008). The prevalence of diabetes (undiagnosed and diagnosed) is estimated to similarly increase from 14% in 2007 up to 33% by 2050 (Boyle et al., 2010). Current reports place the prevalence of NAFLD between 20 and 30% (Wieckowska and Feldstein, 2008), though estimates range from 17 to 40% (Hardwick et al., 2010). In obese populations, this prevalence increases to 90% (Machado et al., 2006), making the projected increase in obesity particularly concerning.

Although considered to be primarily an adult disease, the alarming increase in childhood obesity has coincided with an increasing recognition of the prevalence of pediatric NAFLD (Schwimmer et al., 2006; Lavine et al., 2010; Patton et al., 2006). NASH as a cause of chronic liver dysfunction in obese children was first reported in the early 1980s (Moran et al., 1983). Disturbingly, patients as young as 9 years have been reported with cirrhosis (Kader et al., 2008). In pediatric patients, the prevalence of NAFLD is estimated to be 9.6%, and the rate is higher among adolescents (17.3%) than infants (0.7%) (Schwimmer et al., 2006). These findings are quite similar to the observed increase in the prevalence of insulin-resistant diabetes seen in adolescents (Maclaren et al., 2007). As with adults, the of NAFLD is increased among obese children (38%) (Schwimmer et al., 2006). However, though only 10% of adult NAFLD patients have progressed to the inflammatory, fibrogenic stage of NASH, it is estimated that 26% of pediatric cases have already progressed to NASH (Nobili et al., 2006).

Racial and ethnic differences are observed among patients with NAFLD, likely due to the varied prevalence of the two major risk factors in NAFLD: obesity and type 2 diabetes. Both obesity and type 2 diabetes are more prevalent among non-Hispanic black and Mexican-American patients, compared to non-Hispanic whites (Flegal et al., 1998, 2002, 2010; Harris et al., 2002). Metabolic syndrome, which is a well-established risk factor of NAFLD, is seen more often in Hispanics than non-Hispanic blacks and whites (Ford et al., 2002), and Hispanic males have a higher percentage of body fat than white and black males (Ellis, 1997). NAFLD also appears to be more common among Hispanic children, with higher prevalence in non-Hispanic whites, compared to non-Hispanic blacks (Loombaet al., 2009).

Histology/etiology

Steatosis, also referred to as simple fatty liver or nonalcoholic fatty liver (NAFL), is generally defined as hepatic triglyceride accumulation exceeding 5% by weight (Neuschwander-Tetri and Caldwell, 2003). This lipid increase can appear as macrovessicular, microvessicular, or a combination of the two and is typically observed in zone 3 hepatocytes.

A diagnosis of NASH requires evidence of steatosis, lobular inflammation, and hepatocellular damage and, most often, occurs in zone 3 hepatocytes. This damage may take the form of ballooning degeneration, Mallory-Denk bodies, apoptosis, and/or necrosis (Tiniakos et al., 2010). Inflammatory infiltrates may include lymphocytes, eosinophils, and polymorphonuclear leukocytes, in addition to the resident Kupffer cell macrophages. Additionally, fibrosis may be present even in noncirrhotic NASH, also originating in zone 3.

This fibrosis can progress to portal and periportal regions and, eventually, reach bridging fibrosis and cirrhosis (Tiniakos et al., 2010).

Pediatric and adult NAFLD are predominantly the same disease, and pediatric NAFLD leads to an increased risk for lifelong severe liver disease (Roberts, 2007). In comparison to adult NASH, histological findings (including steatosis, inflammation, and fibrosis) from pediatric patients maybe localized to zone 1 hepatocytes (Schwimmer et al., 2005). This distinct histological picture has been termed “type 2 NASH” (Roberts, 2007).

Steatosis occurs due to a dysregulation of triglyceride synthesis and transport. Sources of these accumulated lipids include increased fatty acid influx (from both diet and peripheral tissues), increased *de novo* lipogenesis, and decreased triglyceride removal (VLDL production and secretion). It is estimated that 60% of hepatic fat content comes from circulating fatty acids, not dietary content (Donnelly et al., 2005). Hyperinsulinemla and hyperglycemia cause activation of lipogenic transcription factors, including sterol regulatory binding protein-1 (SREBPl), which increase *de novo* lipogenesis and inhibit free fatty acid oxidation. Additionally, lipid export from hepatocytes may be impaired due to defective incorporation of triglycerides into apolipoprotein B, decreased apolipo-protein B synthesis, or excretion (Jou et al., 2008).

Hepatic steatosis does not universally result in liver injury and requires a second “hit,” potentially caused by oxidative stress or inflammation, to progress to NASH (Day and James, 1998). Impaired mitochondrial function may lead to activation of lipid catabolic pathways that generate reactive oxygen species, causing lipid peroxidation of the mitochondrial membrane phospholipids, leading to an additional decrease in mitochondrial function and increased oxidative stress in the cell (Browning and Horton, 2004). Cytokine and adipokine signaling from visceral adipose tissue has been well established as a key player in the progression of NAFLD. It is currently hypothesized that the oxidative and metabolic stresses, in combination with the cytokine dysregulation, eventually result in hepatocyte death, resulting in further inflammatory signaling and an induction of hepatic stellate cells in a librotic repair response (Jou et al., 2008).

Diagnosis

Most patients with fatty liver are asymptomatic and undiagnosed, even in advanced stages of the disease. Even in suspected cases of NAFLD, for many patients, the precise stage of the disease (i.e., simple steatosis vs. NASH vs. severe fibrosis) is unknown. This lack of clinical information is due to the inadequacies of current diagnostic methods.

NAFLD is often suspected after findings of elevated aminotransferases in the absence of significant alcoholic consumption, especially in the presence of other features of the metabolic syndrome. However, normal serum aminotransferase tests can be seen in patients with both steatosis and NASH (Mofrad et al., 2003; Ipekci et al., 2003). Indeed, it is reported that two thirds of NASH patients may have normal aminotransferase levels at any given time (Oh et al., 2008; Delgado, 2008; Wieckowska and Feldstein, 2008). Kunde et al. investigated the accuracy of NASH diagnosis by serum alanine aminotransferase (ALT) levels in women undergoing gastric bypass surgery (Kunde et al., 2005). They compared two different reference laboratory cutoffs for “normal” ALT levels; the previous guideline of 30 U/L and the new lower level of 19 U/L that was suggested to aid in the diagnosis of NAFLD. Importantly, the researchers reported that the diagnostic utility of serum ALT remained poor, even at the new lower cutoff. Sensitivity and specificity of serum ALT levels were found to be 42 and 80% (ALT >30 U/I.) versus 74 and 42% (ALT >19 U/L). These and other studies (Lizardi-Cervera et al., 2006; Amarapurka et al., 2006; Amarapurkar and Patel, 2004; Chen et al, 2006; Fracanzani et al., 2008; Sorrentino et al., 2004; Mofrad and

Sanyal, 2003; Uslusoy et al., 2009) illustrate the need for a more effective diagnostic measure for NAFLD, especially for the staging of NASH.

Several imaging techniques have been used with success in diagnosing NAFLD. These include ultrasonography, computerized tomographic (CT) scanning, and magnetic resonance imaging (MRI), each of which is effective at detecting hepatic steatosis. Of these methods, ultrasonography is preferred because of its lower cost and accessibility. However, it has several limitations. Sensitivity is high (80%) in patients with >30% steatosis, but drops to 55% with steatosis <19% (Wieckowska and Feldstein, 2008). Similarly, in morbidly obese patients, sensitivity drops to 49% (Mottin et al., 2004). Similar decreases occur with respect to specificity. Additionally, ultrasonography is unable to provide a quantitative measure of the degree of lipid accumulation. Both MRI and CT scans provide an accurate quantitation of steatosis, yet the higher costs are prohibitive. The most important limitation of each of these imaging methods is the inability to distinguish between steatosis and NASH. A more recent technique, transient elastography, measures liver stiffness and may be effective in assessing the level of hepatic fibrosis in later stages of NAFLD. However, a recent study found an increased failure rate in overweight and obese patients, which may limit the effectiveness of this technique in NAFLD (Foucher et al., 2006).

Liver histology remains the gold standard in diagnosing NAFLD, as it is able to assess steatosis, fibrosis, and inflammation. Importantly, this ability to stage and grade NAFLD allows a differentiation between simple steatosis and NASH. As mentioned previously, the principle features of NASH include macrovesicular steatosis, lobular inflammation, and ballooning degeneration. In addition to these criteria, liver biopsies also reveal the degree of liver damage and any changes in overall liver architecture (Wieckowska and Feldstein, 2008). However, there are also limitations to this procedure; chief among them is the invasive nature of the technique. Studies have indicated significant risks and complications associated with liver biopsies, including pain, major bleeding, and death. It has been estimated that 1–3% of patients may require hospitalization after a liver biopsy (Bravo et al., 2001), though, in at least one study, biopsy-related mortality occurred in over 1% of patients (Thampanitchawong and Piratvisuth, 1999). Other identified limitations of liver biopsies include the subjective nature of the histological analysis and the possibility of sampling error due to the relatively small sample size. In spite of these concerns, liver biopsy remains the only proven, reliable method of diagnosing NASH.

The significant underdiagnosis of fatty liver disease and inability to easily track disease progression presents two important points for consideration. First, there are an enormous number of patients in the U.S. population in whom NAFLD may alter DME activity and drug pharmacokinetics. These unsuspecting patients may be at an increased risk for adverse drug reactions or other toxic events. Second, studies on the effect of NAFLD, to date, have been hampered by the difficulty in indentifying and correctly staging the disease. Because of this, the majority of the studies presented in this review are from animal models of the disease. There is a clear clinical need for additional investigations aimed at developing more efficient methods of identifying these patients, as well as better characterizing the metabolic changes associated with the disease.

Effects

NAFLD in general and NASH in particular are increasingly recognized as serious diseases. NASH is the most common cause of cryptogenic cirrhosis (Clark and Diehl, 2003; Kojima et al., 2006), and it is estimated mat 30-50% of NASH patients will progress to cirrhosis within 10 years (Jou et al., 2008). Because of this, NASH is reported to be the underlying cause of 10% of liver transplants (Preiss and Sattar, 2008). Additionally, NASH is

responsible for an estimated 13% of all hepatocellular carcinoma cases (Marrero et al., 2002; Bugianesi et al., 2002).

In addition to these pathological defects, it has been established that various liver diseases can affect the metabolism and disposition of therapeutic drugs due to alterations in the expression and activity of DMEs. For example, models of sepsis and viral hepatitis exhibit altered cytochrome (CYP)-mediated biotransformation (Morgan, 2001). This downregulation in CYP activity has also been observed in human subjects treated with lipopolysaccharide (LPS), a model of Gram-negative sepsis (Shedlofsky et al., 1994).

NAFLD also modulates the expression and activity of a number of DMEs and may result in altered pharmacologic efficacy or adverse drug reactions. Altered pharmacokinetics have been reported in obese subjects with respect to hormonal contraceptives (Edelman et al., 2010; Skouby, 2010), as well as a number of other drugs (Lloret et al., 2009). Pediatric NAFLD patients have been observed to have altered acetaminophen pharmacokinetics, compared to normal, healthy children (Barshop et al., 2011). A recent study investigating the effect of NASH on the pharmacokinetics of several cationic drugs found altered intrinsic elimination clearance due to increased expression of specific metabolic enzymes (Li et al., 2011). Animal models of NAFLD have demonstrated decreased metabolism and increased toxicity from the antipsychotic drugs, clozapine (Zhang et al, 2007) and haloperidol (Hanagama et al., 2008). Additionally, patients with NAFLD have been reported to have increased risk for adverse drug reactions, specifically drug-induced liver disease (Tarantino et al., 2007, 2009).

Modeling human disease

As mentioned previously, the only definitive method of staging NAFLD is a liver biopsy. This presents a significant complication to the study of human fatty liver disease at several levels, including identifying patients for study, obtaining tissue samples, and tracking disease progression. Further, human DME expression and activity can vary widely between patients due to a number of variables (e.g., genetic polymorphism, diet, xenobiotic exposure, age, and so on) (Guengerich, 2006; Gomez-Lechon et al., 2009). As a result of these limitations, the majority of human NAFLD studies employ one of two tissue sources: cadaveric organs and bariatric surgery patients. Postmortem tissue samples provide sufficient material for analysis of mRNA and protein expression, as well as activity, though a detailed medical history of the patient is often lacking. The patient population undergoing bariatric surgery (i.e., morbidly obese patients), have a much higher rate of both NAFLD and NASH (Lazo and Clark, 2008). The routine intraoperative liver biopsies performed during bariatric surgery allow a detailed determination of NASH status in these patients (Tanaka et al., 2006; Dolce et al., 2009).

Because of the difficulty in identifying properly diagnosed NAFLD patients, as well as the ethical and practical issues with obtaining liver samples for analysis, the majority of studies on NAFLD gene alterations have employed animal models. Although some of these models are of limited accuracy in relation to either histological outcome or disease context (reviewed by Larter and Yeh, 2008; Anstee and Goldin, 2006), a detailed presentation of the various benefits and faults of each is not the focus of this review. However, a brief description of the models used in the studies described below may prove beneficial to properly compare results between models and species. Though NAFLD studies using nonrodent species have been described (Leclercq et al., 1998), the vast majority of research has been performed in rat and mouse models.

These rodent models are genetic, dietary, or a combination of the two. In both rats and mice, the most common genetic models involve dysregulation of leptin signaling, leading to

hyperphagia and obesity. Obese Zucker (*fa/fa*) rats and *db/db* mice are deficient in the leptin receptor, whereas *ob/ob* mice are deficient in leptin itself. Though these models exhibit insulin resistance and obesity, their liver pathology rarely progresses beyond steatosis to NASH without a second insult (Larter and Yeh, 2008). Because of this, drug-metabolism data presented from these genetic models can be assumed to correlate with a human diagnosis of simple steatosis.

To stimulate the progression to NASH, a dietary model is often used. The most well-characterized model of rodent NASH is a methionine-choline–deficient (MCD) diet, which rapidly induces steatohepatitis with a liver histopathology closely recapitulating the human condition. However, in contrast to human NASH, animals fed the MCD diet experience significant weight loss, hypoin-sulinemia, and are insulin sensitive. Despite these shortcomings, in our experience, the MCD diet accurately models the expression changes of a majority of ADME, genes.

An alternate dietary model, the high-fat diet, has been used to more closely recapitulate the modern “Western-diet.” However, rodents adapt to high-fat feeding and may take several months to progress to NASH. Additionally, the composition of the experimental chow may vary a great deal in a number of constituents, with varying experimental results. In the absence of a stated hepatic histological staging, it is difficult to properly assign these models to steatosis or NASH (Larter and Yeh, 2008). Additional animal models employed include dietary orotic acid and forced intragastric feeding, which result in steatosis and steatohepatitis, respectively (Zhang et al., 2007; Deng et al., 2005).

As mentioned above, each of the animal models currently in use have limitations that may complicate the extrapolation of disease results to human patients. It is important to also note that in certain cases, the mechanisms of enzyme regulation may differ significantly between species. Despite these shortcomings, animal models provide a valuable tool to investigate the effects of fatty liver.

Drug metabolism in NAFLD

Metabolism is the major clearance mechanism for the most frequently prescribed drugs (Williams et al., 2004), and the liver is the major organ of drug metabolism. A variety of enzymes with overlapping substrate specificity is expressed in the liver and are commonly divided into phase I (i.e., oxidizing) and II (i.e., conjugating) DMEs. Phase I enzymes belong predominantly to the cytochrome p450 family, whereas major phase II enzymes include glucuronosyltransferases, sulfotransferases, and glutathione transferases.

Below, we have compiled the results of published animal and clinical studies of NAFLD and obesity, where DME expression or activity was investigated. The stated focus of several of these animal studies was obesity (or diabetes), and liver histology or NAFLD status was not obtained as part of the original study. However, the models employed have been demonstrated elsewhere to induce various stages of NAFLD and have, therefore, been included. We have attempted to simplify the presentation of these published studies by grouping results together by enzyme families, rather than by experimental model of patient characteristics. Likewise, rather than comparing the magnitude of DME alterations, we have chosen to focus on identifying a consistent direction (i.e., induction or inhibition) of DME changes in the progressive stages of NAFLD. The details and results of these studies have been compiled in the included tables (Tables 1-8).

Phase I

Cytochrome P450s—A recent study of the 200 most often prescribed drugs found that two thirds of hepatically cleared drugs were metabolized by CYPs (Williams et al., 2004). These enzymes belong to three families (*CYP1, CYP2,* and *CYP3*), with several isoforms within multiple subfamilies. CYP3A is the predominant hepatic CYP, both in terms of relative expression and the number of relevant substrates. In terms of the percent of drugs metabolized, CYP2C9, 2D6, 2C19, and 1A2 follow CYP3A. Other enzymes, such as 2A6 and 2E1, are collectively responsible for only 6% of clinically relevant drugs (Zanger et al., 2005). Information on the effects of NAFLD on drug-metabolizing CYP enzymes was found for CYP1A2, 2A, 2B, 2C, 2D, 2E, and 3A.

CYP1A2—CYP1A2 constitutes approximately 13% of hepatic CYP enzymes and metabolizes some 15% of therapeutic drugs. Substrates for this enzyme are varied and include adenosine receptor inhibitors, analgesics, antiarrhythmic drugs, anticancer drugs, anticoagulants, antidepressants, antihistamines, antihypertensive drugs, antipsychotics, β-blockers, cyclooxygenase-2 inhibitors, anesthetics, and drugs from several other classes (reviewed by Zhou et al., 2009).

The downregulation of CYP1A2 in NAFLD is one of the more consistent findings in studies of DME expression and activity. In several different rat models of steatosis, mRNA and protein were significantly decreased (Zhang et al., 2007; Hanagama et al., 2008). Suh et al. (2005) reported an initial increase in Cypla2 mRNA expression in obese Zucker rats at 6 weeks, but by 12 weeks, the expression was significantly decreased over lean controls. The sole study to detect alterations in Cypla2 in a rat model of NASH employed intragastric forced feeding and resulted in a modest increase in mRNA expression (Baumgardner et al., 2008). Results in mouse models paralleled that of the rat, with several groups employing both genetic and dietary models of steatosis exhibiting decreased mRNA, protein, and/or activity (Yoshinari et al., 2006; Kirpich et al., 2010; Roe et al., 1999), though others failed to detect this decrease (Watson et al., 1999; Barnett et al., 1992; Fisher et al., 2008). The lone study to find an increase in Cypla2 activity found protein levels unchanged (Koide et al., 2010).

Three groups have also reported a downregulation of CYP1A2 in human NAFLD. Greco et al. (2008) detected CYP1A2 as a significantly decreased gene in microarray studies of NAFLD patients. Using hepatocytes isolated from human liver grafts of patients with fatty liver disease, Donato et al. (2006) observed a 44% reduction in CYP1A2 activity. Our own studies, using postmortem liver samples, revealed a significant decrease in both protein and activity of CYP1A2 with the progression of NAFLD (Fisher et al., 2009).

CYP2A—CYP2A6 (reviewed by Di et al., 2009) makes up a small fraction of the total hepatic CYPs (4%) and metabolizes approximately 3% of therapeutic drugs. These include anticonvulsants, anesthetics, and anticancer drugs, as well as nicotine. In part because of this comparatively small role in drug metabolism, relatively few studies in either humans or animal models have investigated CYP2A in NAFLD.

In animal studies, Weltman et al. (1996) reported decreased enzymatic activity in MCD-fed rats, whereas Watson et al. (1999) observed increased activity in *ob/ob* mice. Studies in human hepatocytes are similarly conflicting, with increased CYP2A6 activity in human hepatocytes isolated from fatty liver grafts and decreased activity in free fatty acids-treated healthy hepatocytes (Donato et al., 2006). Rubio et al. (2007) found CYP2A6 among downregulated hepatic genes in bariatric surgery patients with NASH. Our own studies, using human liver samples, found increased expression both of CYP2A6 mRNA and protein, as well as increased activity with NAFLD progression (Fisher et al., 2009).

CYP2A6 activity is elevated in patients with other inflammatory liver diseases, including hepatitis, primary biliary cirrhosis, and alcoholic cirrhosis (Fisher et al., 2009).

CYP2B—CYP2B6 accounts for 6% of total CYPs in the liver and metabolizes, to some extent, approximately 10% of therapeutic drugs. Substrate specificity for this enzyme overlaps significantly with several other CYP2 family members, and most substrate drugs are more extensively metabolized by these enzymes. The primary interest in CYP2B6 is its induction by a variety of microsomal inducers and its coregulation with CYP3A4 (Mo et al., 2009).

Published studies in mouse models do not allow a clear interpretation of the effect of NAFLD on Cyp2b10. Whereas some studies in genetically steatotic mice reported increased Cyp2b10 expression and activity (Yoshinari et al., 2006; Watson et al., 1999), others observed either no change (Barnett et al., 1992; Fisher et al., 2008) or decreased expression (Kirpich et al., 2010). Further complicating the picture, Cheng et al. (2008) reported increased expression in *ob/ob* female mice and decreased expression in *ob/ob* male mice.

Few studies in human patients have reported on the effects of NAFLD on CYP2B6 expression. Whereas Fisher et al. (2009) found NAFLD progression increased CYP2B6 mRNA in the absence of any effect on protein or activity, two separate groups reported decreased mRNA expression in NASH livers, when compared to the simple fatty liver (Stepanova et al., 2010; Yoneda et al., 2008).

CYP2C—Several isoforms of the CYP2C family exist in the human liver, including 2C8, 2C9 (rat homolog Cyp2c11, mouse homolog Cyp2c29), and 2C19. These three human isoforms together account for approximately 20% of total hepatic CYP content (Hewitt et al., 2007) and are able to metabolize over one half of commonly prescribed drugs (Nebert and Russell, 2002). These drug substrates include anticonvulsant drugs, anticoagulants, antidiabetic drugs, proton pump inhibitors, anticancer drugs, and nonsteroidal anti-inflammatory drugs (NSAIDs). As with *CYP2B6,* members of the *CYP2C* family are inducible by a number of compounds, including therapeutic drugs (Chen and Goldstein, 2009).

Several studies employing rat NAFLD models have reported decreased expression of the CYP2C9-homolog, Cyp2c11, at the mRNA (Hanagama et al., 2008; Kim et al., 2004a) and protein (Zhang et al., 2007) levels in steatotic rats, as well as in MCD-fed rats (Lickteig, 2007). Decreased Cyp2c11 activity has also been reported (Weltman et al., 1996). The *db/db* mouse model revealed unchanged total Cyp2c protein, though mRNA levels of Cyp2c29 were elevated (Yoshinari et al., 2006).

In contrast to the uniform decrease seen in rats, human CYP2C9 expression appears unchanged in NAFLD (Donato et al., 2006; Fisher et al., 2009). However, even in the absence of elevated expression, CYP2C9 activity was significantly and consistently increased in NAFLD progression (Fisher et al., 2009). Whereas the CYP2C isoform, CYP2C8, exhibited no change during the progression of NAFLD, CYP2C19 protein expression and activity were decreased (Fisher et al., 2009). No reports on CYP2C8 and CYP2C19 homologs in experimental NAFLD have been published.

CYP2D6—CYP2D6 makes up only 2–8% of total hepatic CYP content, yet it metabolizes 25% of clinical drugs, including antidepressants, neuroleptics, opioids, antiemetics, antiarrhythmics, β-blockers, antihistamines, and anti-HIV drugs (reviewed by Wang et al., 2009). CYP2D6 is significantly polymorphic, with ultrarapid, extensive, intermediate, and poor metabolizing phenotypes represented in the population. Few published studies

document changes in CYP2D6 during NAFLD. Whereas Donato et al. (2006) reported a significant downregulation of enzymatic activity in hepatocytes treated with increasing amounts of free fatly acids, our studies in human liver samples failed to reveal significant changes in either expression or activity (Fisher et al., 2009).

CYP2E1—CYP2E1 is one of the most well-conserved DMEs, whose drug substrates include several anesthetics, as well as acetaminophen, phenobarbital, fluoxetine, theophylline, and chlorzoxazone (Tanaka et al., 2000). Whereas CYP2E1 plays a relatively minor role in drug metabolism, it plays a major role in chemical toxicity and carcinogenesis. Nondrug substrates include alcohol, acetone, benzene, fatty acids, carbon tetrachloride, and nitrosamines (Lu and Cederbaum, 2008). Induction of both protein and activity appear to occur through increased stabilization of substrate-bound enzyme, often without increased mRNA expression (Gonzalez, 2007).

CYP2E1 is, perhaps, the most studied CYP enzyme in relation to NAFLD and was the first enzyme documented to be modulated in clinical fatty liver disease (Weltman et al., 1998). The majority of human studies have reported increased expression and activity of CYP2E1, and this increase is hypothesized to play a role in NAFLD pathogenesis (Gomez-Lechon et al., 2009). Interestingly, in a number of mouse models, Cyp2e1 expression and activity were decreased (Enriquez et al., 1999; Deng et al., 2005; Watson et al., 1999; Ito et al., 2007; Cheng et al., 2008). Others failed to observe any change (Donthamsetty et al., 2008; Yoshinari et al., 2006; Roe et al., 1999; Barnett et al., 1992; Ito et al., 2006). Relatively few studies reported increases in Cyp2el; in *ob/ob* females (but not males), in steatotic mice (but not in NASH mice), in mice fed a high-fat diet, and in mice fed an MCD diet (Ito et al., 2007; Roe et al., 1999; Mantena et al., 2009; Leclercq et al., 2000). Results in rat studies reveal a more consistent increase in Cyp2el activity and expression in MCD diet fed rats (Weltman et al., 1996), in those fed a high-fat diet, including intragastric overfeeding (Osabe et al., 2008; Khemawoot et al., 2007; Lieber et al., 2004; Baumgardner et al., 2008; Li et al., 2011), and in obese Zucker rats (Khemawoot et al., 2007). Two studies reported decreases in Cyp2e1, in obese Zucker animals, and orotic acid treatment (Zhang et al., 2007; Enriquez et al., 1999).

Researchers have observed human CYP2E1 upregulation in morbidly obese patients (Emery et al., 2003), in general NAFLD (Kohjima et al., 2007), and in NASH (Baker et al., 2010; Weltman et al., 1998; Videla et al., 2004; Chalasani et al., 2003; Orellana et al., 2006). Chtioui et al. (2007) reported no difference in CYP2E1 activity between steatotic livers and those with NASH, with activity correlated to severity of steatosis, instead of disease progression. This is in agreement with findings by Emery et al. (2003), as well as the observation that immunohistochemistry staining localizing CYP2E1 protein expression to the hepatocytes was most affected by lipid accumulation (zone 3) (Weltman et al., 1998; Bell et al., 2010). However, several other studies found CYP2E1 protein and activity unchanged in patients with simple fatty liver (Prompila et al., 2008; Donato et al., 2006; Videla et al., 2004; Orellana et al., 2006). CYP2E1 levels and activity are decreased after dietary restriction and bariatric surgery (Bell et al., 2010; Leclercq et al., 1999). Two studies have observed decreased CYP2E1 mRNA expression in NAFLD, though decreased activity has not been reported (Fisher et al., 2009; Nakamuta et al., 2005)

CYP3A—The *CYP3A* family includes several isoforms (e.g., 3A4, 3A5, 3A7, and 3A43), though CYP3A4 appears to be the major enzyme in drug metabolism. CYP3A4 is the most abundant CYP enzyme in the liver and, alone, accounts for the metabolism of over 50% of drugs (Hewitt et al., 2007). The structurally diverse substrates of CYP3A4 include drugs from almost all classes (reviewed by Zhou, 2008). CYP3A4 activity is highly variable, with

pharmacologic inhibition and induction reported with numerous drugs and other chemicals, including its own substrates (Zhou, 2008).

Due to the major role played by CYP3A in drug metabolism, a number of investigators have studied how this enzyme is modulated by NAFLD. Rat models, to date, have predominantly observed decreased expression or activity of Cyp3a, including both steatosis (Zhang et al., 2007; Osabe et al., 2008; Hanagama et al., 2008; Suh et al., 2005; Kim et al., 2004a) and NASH (Weltman et al., 1996), though increased expression of several Cyp3a isoforms have been observed in rat NASH models, using forced intragastric feeding (Baumgardner et al., 2008; Li et al., 2011). Interestingly, two independent studies observed temporal differences in the regulation of Cyp3a in NAFLD, with decreased expression at 2 weeks, increased expression at 6 and 8 weeks, and decreased expression again at 12 weeks (Osabe et al., 2008; Suh et al., 2005). Studies in *ob/ob* and *db/db* mice failed to detect any change in Cyp3a activity (Yoshinari et al., 2006; Watson et al., 1999; Roe et al., 1999; Barnett et al., 1992). Results in mice fed a high-fat diet were not consistent (Koide et al., 2010; Kirpich et al., 2010; Cheng et al., 2008; Kim et al., 2001b), whereas the only study in a NASH mouse model observed increased expression (Fisher et al., 2008).

Three studies have reported decreased activity of CYP3A4/5 in NAFLD patients (Weltman et al., 1998; Donato et al, 2006, 2007). Bell et al. (2010) investigated the effect of bariatric surgery on protein expression of CYP3A4/5 and CYP2E1. Whereas they observed a significant decrease in CYP2E1 expression, CYP3A4/5 expression was unchanged. In our recent study, we observed a decreasing trend in CYP3A4/5 expression and activity, though neither reached statistical significance (Fisher et al, 2009).

Minor phase I enzymes—Although the majority of phase I metabolism is performed by CYP enzymes, a number of additional enzymes play a minor role in drug and xenobiotic metabolism. NAD(P)H quinoneoxidoreductase 1 (NQOl; NAD(P)H dehydrogenase, quinone 1) acts to detoxicate quinones, for example, the toxic acetaminophen metabolite, NAPQI. Nqol expression is consistently increased in models of NAFLD. Mouse models of both steatosis (Cheng et al., 2008) and NASH (Fisher et al., 2008) reported increased Nqol expression. Whereas Kim et al. (2004a) reported slightly decreased expression in obese Zucker rats, we observed an increase in both the expression and activity in MCD-diet-fed rats (Lickteig et al., 2007). Our recently published findings on the effect of human disease on antioxidant genes found significantly increased mRNA, protein, and activity in the progression of NAFLD (Hardwick et al., 2010). Hemeoxygenase 1 (HO1), though not directly involved in drug metabolism, is another important cyto-protective enzyme. HOI is often coordinately regulated with NQOl and is increased in models of steatosis and NASH (Lickteig et al., 2007; Cheng et al., 2008).

Two additional enzymes detoxicate the reactive intermediates formed during drug metabolism: epoxides and aldehydes. Microsomal epoxide hydrolase (mEH) plays a major role in the hydrolysis of epoxides formed during drug and xenobiotic metabolism. Similarly, aldehyde dehydrogenase metabolizes acetaldehyde, produced by ethanol oxidation, to form acetate. The expression of both enzymes was altered in experimental NAFLD. mEH was upregulated in a rat model of NASH (Lickteig et al., 2007), and several isoforms of ALDH were upregulated in mice fed high-fat diets (Kim et al., 2004b; Lee et al., 2010).

Phase II

Sulfotransferases (SULT)—SULT enzymes are involved in the metabolism of therapeutic drugs and endogenous hormones. Drug-metabolizing SULTs are cytosolic and belong to *SULT1* and *SULT2* families (Nowell and Falany, 2006). Whereas SULTs are the major detoxication enzyme in the developing liver, in adult livers, they account for the

metabolism of less than one fourth of conjugated drugs (Jancova et al., 2010). Common SULT substrates include acetaminophen, albuterol, terbutaline, methyldopa, and hormonal contraceptives (Liston et al., 2001; Edelman et al., 2010).

Early studies in obese overfed rats reported decreased formation of acetaminophen sulfonate, though NAFLD status was not investigated (Corcoran et al., 1987; Corcoran and Wong, 1987). Few studies have reported on the effect of NAFLD on SULT expression or activity. Cheng et al. (2008) observed an increase in Sult2al/2 expression in *ob/ob* males, with no change in females. Koide et al. (2010) reported a decrease in Sult2a1 protein expression and activity in mice fed a high-fat diet, though no change was detected in Sult1a1 in the same animals. Studies in obese Zucker rats also found SULT activity unaffected by NAFLD (Chaudhary et al., 1993).

In human patients, Younossi et al. (2005a) reported SULT1A2 among genes downregulated in NASH. Interestingly, Stepanova et al. (2010) compared hepatic gene expression between Caucasian and African-American patients with steatosis or NASH. SULT1A1 expression was significantly downregulated with the progression to NASH, though only in African Americans.

UDP glucuronosyltransferases (UGTs)—Glucuronide conjugation is the major method of phase II conjugation and plays a key role in conjugating clinical drugs for processing and elimination from the body. Several NSAIDs and opioids are excreted primarily as glucuronide conjugates, as are certain anxiolytics, antidepressants, and antipsychotics (reviewed by Liston et al., 2001). UGTs are also involved in the metabolism of several hormonal contraceptives (Liston et al., 2001; Edelman et al., 2010). Two enzymes families, *UGT1A* and *UGT2B,* are clinically important in humans, with several distinct gene products of widely varying substrate specificity in each family. *UCT1A* family members share common exons (2-5). Loss of function mutations in these exons can lead to Crigler-Najjar syndrome (Bock, 2010). *UGT2B* family members are particularly important, both due to protein levels (UGT2B4, UGT2B10) and number of drugs metabolized (UGT2B7) (Bock, 2010).

No human studies have reported changes in UGT expression in NAFLD. In animal models, published results are fairly consistent. Obese Zucker rats exhibited decreased mRNA expression of Ugt1a1, 1a6, and 2a1 (Kim et al., 2004a), though others observed increased glucuronidation in the same model (Chaudhary et al., 1993). Similarly, rats fed a high-fat diet had decreased protein levels of Ugt1a1, 1a6, 1a7, and 2b1 (Osabe et al., 2008). Watson et al. (1999) observed no change in Ugt activity in *ob/ob* mice. Ugt 1a9 mRNA levels were observed to decrease in mice with steatosis (Kirpich et al., 2010), though protein and activity were unaltered (Koide et al., 2010). Ugt2b activity was reportedly increased in high-fat-diet-fed mice, though expression was unchanged or even decreased (Koide et al., 2010; Kirpich et al., 2010).

Glutathione—The glutathione antioxidant system is responsible for the conjugation of nucleophilic glutathione (GSH) to electrophilic compounds, including drugs and drug metabolites. This conjugation is performed by glutathione *S*-transferase (GST) enzymes, grouped into five classes: alpha, mu, pi, theta, and zeta (Hayes et al., 2005). Glutathione-conjugation activity can be modulated through changes in the expression of GSTs, in GSH levels, or in the expression of enzymes that synthesize GSH. Whereas glutathione synthetase (GSS) is involved in the final step, the rate-limiting step in GSH synthesis is catalyzed by glutamylcysteine ligase (GCL), which is composed of a catalytic (GCLC) and a modifier (GCLM) subunit (Lu, 2009).

Glutathione *S*-transferases—The impact of NALFD on GST expression and activity appears to be isoform and, possibly, species specific. Members of the alpha family showed increased expression in *ob/ob* mice (Sharma et al., 2010), but expression was decreased in mice fed a high-fat diet and in obese Zucker rats (Kirpich et al., 2010; Kim et al., 2004a). Two human studies have reported increases in GSTA expression. We recently reported an increase in the expression of GSTA1, A2, and A4 in NAFLD progression (Hardwick et al., 2010). Younossi et al. observed increased GSTA4 expression in NASH, though the parallel increase in a non-NAFLD obese control group may indicate an association with obesity, rather than NAFLD (Younossi et al., 2005b).

Mouse studies on the effect of NAFLD on the mu family of GSTs have all employed high-fat diets to induce steatosis. GSTm1, m2, m3, and m6 expression has been observed to increase (Lee et al., 2010; Kim et al., 2004b) or to decrease (Kirpich et al., 2010) by different groups. In human studies, we have observed that NAFLD progression significantly increases the expression of GSTM1 and M3, but saw a contrasting decrease in overall GSTM protein expression (Hardwick et al., 2010). Yoneda et al. (2008) reported a decrease in GSTM1 expression with the progression from steatosis to NASH. Similarly, GSTM1, 2, 4, and 5 were found among genes downregulated in steatosis (Younossi et al., 2005a) and NASH (Rubio et al., 2007). Interestingly, ethnicity may have a significant impact on GSTM expression in NAFLD, as Stepanova et al. (2010) reported that GSTM2, M4, and M5 are all increased more in African Americans with NASH than in Caucasians with the same disease. Finally, whereas GSTP1 mRNA was downregulated in mice fed a high-fat diet (Kirpich et al., 2010), our human studies found both mRNA and protein expression significantly increased (Hardwick et al., 2010).

The majority of investigations into GST activity in NAFLD have found decreased enzymatic activity, including studies of both *ob/ob* mice (Roe et al., 1999; Barnett et al., 1992) and human liver samples (Hardwick et al., 2010). Koide et al. (2010) reported increased activity in high-fat-diet-fed mice, and other groups have found no change in NAFLD models (Watson et al., 1999).

GSH content and synthesis—A number of studies have observed hepatic depletion of GSH content in NAFLD. GSH levels were unchanged in obese Zucker rats, when compared to liver weight (Chaudhary et al., 1993) in *ob/ob* mice (Watson et al., 1999) and mice fed a high-fat diet (Ito et al., 2006). Other mouse studies have observed a depletion of total GSH in both steatosis and NASH (Ito et al., 2007; Barnett et al., 1992; Lee et al., 2010), as have studies in human NAFLD patients (Videla et al., 2004; Hardwick et al., 2010). With the depletion of GSH, there is a concurrent decrease in the ratio between reduced GSH and oxidized GSSG (Lee et al., 2010; Hardwick et al., 2010) in NAFLD, demonstrating the increased oxidative stress inherent in the disease (Pastore et al., 2003). Further, this depletion of hepatic GSH is not due to decreased synthesis, as GSS, GCLC, and GCLM have been found to be unchanged or even increased in NAFLD (Kohjima et al., 2007; Chaudhary et al., 1993; Lickteig et al., 2007; Hardwick et al., 2010; Kim et al., 2004b).

Mechanisms

Investigation into the mechanisms responsible for these NAFLD alterations in drug metabolism are limited, though several potential mechanisms have been proposed. These include modulation by inflammatory mediators, inhibition by free fatty acids, nuclear receptor activation, and oxidative stress signaling.

Cytokines

Insulin resistance and obesity are proinflammatory conditions, and, whereas overt inflammatory infiltration only occurs in later stages of NAFLD, cytokines and inflammatory mediators are observed in all stages of the disorder. Prominent cytokines involved in NAFLD progression include interleukin 1 (IL-1), IL-6, IL-8, and tumor necrosis factor-α (TNFα) (Jarrar et al., 2008; Estep et al., 2009; Wieckowska et al., 2008). The downregulation of CYP activity and expression with inflammation has been well described (Aitken et al., 2006), yet little has been reported on the effects of inflammation on phase II metabolic enzymes. Depletion of Kupffer cells in rat liver slices was shown to correlate with increased acetaminophen glucuronidation (Neyrinck et al., 1999), indicating that cytokines may also downregulate conjugating DMEs in addition to CYP enzymes.

In addition to the potential for inflammatory signaling from endogenous sources, several studies have investigated the role for endotoxemia in the progression of NAFLD (reviewed in Manco et al., 2010). The modulation of DMEs during LPS treatment and bacterial infection has been well documented, though the precise mechanisms are still under investigation (Morgan, 2009). The effects of endotoxemia appear predominantly to downregulate enzyme expression and activity, in contrast to the frequent upregulation seen in several enzymes during NAFLD. Nevertheless, there is a clear potential for LPS-dependent effects on drug metabolism during NAFLD.

Nuclear receptors

CAR/PXR—The expression of many DMEs is modulated through the activity of nuclear receptors. The pregnane X receptor (PXR), known as the steroid and xenobiotic receptor in humans (SXR), along with the constitutive androstane receptor (CAR), are two well-known xenosensors and master regulators of xenobiotic response (Kakizaki et al., 2008). Studies in two mouse models have reported increased mRNA expression of PXR in NAFLD, one of which coincided with increased expression of Cyp3all (Yoshinari et al., 2006; Fisher et al., 2008). Characterized target genes of these receptors include *CYP2B, 2C,* and *3A,* as well as *SULTs* and *UGTs* (Kakizaki et al., 2008), making the modulation of PXR and/or CAR activity an obvious hypothesis for the alterations seen in NAFLD.

Additionally, multiple links have been reported between these xenosensors and the regulation of energy/lipid metabolism (reviewed by Gao and Xie, 2010). Polyunsaturated fatty acids have been shown to modulate the activity of CAR and, to a lesser extent, PXR (Finn et al., 2009). The transcription factorsterol-regulatory element binding protein (SREBP1) is upregulated in obese insulin-resistant patients (PettinelLi et al., 2009), and this factor has been shown to inhibit both PXR and CAR (Roth et al., 2008b). The master energy sensor, AMP-activated protein kinase (AMPK), is responsible for decreasing gluconeogenesis and lipogenesis and appears to be required for CAR activation in the liver (Rencurel et al., 2005, 2006; Shindo et al., 2007). Finally, the insulin-sensitive transcription factor, FOXOl, has been shown to modulate the activity of both CAR and PXR (Kodama et al., 2004). Recent research has also indicated that CAR activation may be protective against NAFLD (Gao et al., 2009; Dong et al., 2009; Roth et al., 2008a; Zhai et al., 2010), though other studies have reported the opposite (Yamazaki et al., 2007).

HNF4α—The nuclear receptor, hepatocyte nuclear factor 4-alpha (HNF4α), is activated by a variety of fatty acids and is responsible for controlling several metabolic pathways, including both fatty acid metabolism and drug metabolism. Reported CYPs regulated by HNF4α include CYP2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 (Jover et al., 2009). Whereas both CAR and PXR are induced by HNF4α, it appears that only CYP2B6

induction by HNF4α can be fully attributed to these increased CAR levels (Kamiyama et al., 2007).

In NAFLD, Yoshinari et al. (2006) observed no significant change in the mRNA levels of HNF4α mRNA in *db/db* mice. Similarly, Sugatani et al. (2006) reported unchanged HNF4α mRNA levels in rats fed a high-fat diet. However, levels of nuclear HNF4α protein were significantly decreased in this rat model. It is possible that the general decrease in total CYP expression observed by many groups is due to an inhibition of HNF4α protein levels in NAFLD.

Oxidative stress signaling—Cells respond to oxidative stress, such as that which occurs in the progression of NAFLD, by upregulating antioxidant genes. This antioxidant response is controlled by a specific transcription factor, NF-E2-rclatcd nuclear factor 2 (Nrf2) (Jaiswal, 2004). Under normal conditions, Nrf2 is negatively regulated by the protein, Keapl, which is responsible for sequestering Nrf2 from the nucleus and aiding in its degradation (Li and Kong, 2009; Zhang, 2006). When a cell undergoes oxidative stress, Nrf2 is released from Keapl and translocates to the nucleus, where it is able to promote the transcription of its target genes. Work from our lab and others have revealed Nrf2 activation in both experimental (i.e., high-fat-diet– or MCD-diet–fed mice) and clinical NAFLD (Fisher et al., 2008; Hardwick et al., 2010; Kim et al., 2004b).

Similarly to CAR and PXR, Nrf2 acts to regulate both xenobiotic responses and energy metabolism. A recent study by Kitteringham et al. (2010) suggested that Nrf2 may be a major regulator of hepatic lipid disposition. This is in addition to its well-known regulation of GSTs, UGTs, SULTs, and GSH production (Shen and Kong, 2009). Nrf2 has been shown to modulate CYP activity as well, including the downregulation of CYP1A2 and the induction of CYP2A5 (Garget al., 2008; Lamsa et al., 2010). Researchers are further examining the interplay between Nrf2 activation and NAFLD progression (Chowdhry et al., 2010; Sugimoto et al., 2010; Zhang et al., 2010; Pi et al., 2010; Shin et al., 2009).

Conclusions

The hepatic disorder known as NAFLD results in significant alterations in the expression and activity of multiple DMEs. Because of the extremely high prevalence of the disease, when considering any drug in clinical use in the United States, it is likely that some patients receiving the drug will have NAFLD. Altered drug metabolism in NAFLD patients may lead to altered pharmacokinetics and increased risk for adverse drug reactions. In reviewing the data currently available in the literature, several categories of responses to NAFLD are observed.

The first category of responses includes enzyme changes that are consistent and uniform across nearly all of the published studies. For example, NAFLD appears to elicit a near-uniform downregulation of CYP1A2 as well as cellular GSH. Drugs significantly metabolized by CYP1A2 or GSH conjugation should be closely monitored during administration to patients where NAFLD is suspected. Additionally, because these changes are consistent across species, rodent models of NAFLD may be of use in identifying potential toxic events associated with these specific alterations.

The second category includes alterations that appear to be dependent upon species, sex, or even ethnicity. The upregulation of CYP2E1 in NAFLD is reported in the majority of human and rat studies, yet mouse studies regularly observe downregulation of this enzyme. DME alterations in NAFLD are also impacted by both race and sex. These findings highlight the importance of carefully considering and controlling for the multiple potential sources of

variability in DME expression and activity. Additional comprehensive investigations into the relative impact of these factors within the presence of NAFLD would be beneficial.

Finally, in the case of most of the clinically relevant DMEs, the effects of NAFLD are unclear, either because of high variability between studies (CYP3A) or because of an insufficient number of studies (SULTs and UGTs). In cases such as these, the use of probe compounds may allow *in vivo* determination of relative metabolic activity and identification of individuals that require personalized dosing regimens. In the progression to this more personalized approach to pharmacotherapy, considerations of drug metabolism and altered pharmacokinetics by chronic diseases, such as NAFLD, are imperative.

Despite the high prevalence of NAFLD, research in regard to the disease effects on hepatic drug metabolism is lacking, especially in human subjects. Though obvious difficulties exist (i.e., identifying clinical subjects, obtaining tissue samples), information about disease-induced variability in drug metabolism and clearance is vital to safe pharmacotherapy.

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Table 1

Table N, Effect of NAFLD on the expression and activity of X″ X being CYP1A2, CYP2E1, and CYP3A.

CYP1A2	Source	mRNA	Protein	Activity	Diagnosis	Model	Study
	Mouse			↔	not reported	ob/ob at 12 weeks	Watson et al., 1999
				↔	not reported	ob/ob at 16 weeks	Barnett et al., 1992
			↓	↓	not reported	Male ob/ob at 8 months	Roe et al. 1999
			↓	↓	not reported	Female ob/ob at 4 and 8 months	Roe et al., 1999
		↔	↓		not reported	db/db at 10 weeks	Yoshinari et al., 2006
			↔	↑	not reported	45% fat for 6 months	Koide et al. 2010
		↓			Steatosis	60% fat for 8 weeks	Kirpich et al. 2009
		↔			NASH	MCD for 8 weeks	Fisher et al., 2008
	Rat	↓			not reported	Obese Zucker at 12 weeks	Suh et al. 2005
		↓			not reported	High fat (details not reported)	Hanagama et al. 2007
		↔	↔		Steatosis	18% butter for 8 weeks	Lickteig, 2007
			↔		not reported	65% fat for 8 weeks	Osabe et al. 2007
			↓		Steatosis	Orotic acid	Zhang et al., 2007
		↑			NASH	Intragastric overfeeding	Baumgardner et al. 2008
		↔	↔		NASH	MCD for 8 weeks	Lickteig, 2007
	Human	↓			Steatosis		Greco et al. 2008
				↓	Steatosis		Donato et al. 2006
		↔	↓	↓	Progression of NAFLD		Fisher et al., 2009

Table 2

Effect of NAFLD on the expression and activity of CYP2A6.

CYP2A6	Source	mRNA	Protein	Activity	Diagnosis	Model	Study
	Mouse			↑		ob/ob at 12 weeks	Watson et al., 1999
	Rat			↓		MCD for 4 weeks	Weltman et al., 1996
	Human	↑	↑	↑	Progression of NAFLD		Fisher et al., 2009
		↓			NASH		Rubio et al., 2007

Table 3

Effect of NAFLD on the expression and activity of CYP2B6.

CYP2B6	Source	mRNA	Protein	Activity	Diagnosis	Model	Study
	Mouse	↓			Steatosis	Male ob/ob at 11 weeks	Cheng et al., 2008
		↑			Steatosis	Female ob/ob at 11 weeks	Cheng et al., 2008
				↑	Not reported	ob/ob at 12 weeks	Watson et al., 1999
				↔	Not reported	ob/ob at 16 weeks	Barnett et al., 1992
			↑	↑	Not reported	db/db @ 10 weeks	Yoshinari et al., 2006
		↓			Steatosis	60% fat for 8 weeks	Kirpich et al, 2009
					NASH	MCD for 8 weeks	Fisher et al., 2008
	Human	↑	↔	↔	Progression of NAFLD		Fisher et al., 2009
		↓			NASH (Caucasians)		Stepanova et al., 2010
		↓			NASH vs. steatosis		Yoneda et al., 2008

Table 4

Effect of NAFLD on the expression and activity of CYP2C.

CYP2C	Source	Isoform	mRNA	Protein	Activity	Diagnosis	Model	Study
	Mouse	total 2C		↔		Not reported	db/db at 10 weeks	Yoshinari et al., 2006
		2C29	↑			Not reported	db/db at 10 weeks	Yoshinari et al., 2006
	Rat	2C11	↓			Not reported	Obese Zucker at 14–16 weeks	Kim et al., 2004a
		2C11	↓			Not reported	High fat (details not reported)	Hanagam et al., 2007
		2C11	↓	↓		Steatosis	18% butter diet for 8 weeks	Lickteig, 2007
		2C11		↓		Steatosis	Orotic acid	Zhang et al., 2007
		2C11			↓	Steatosis	MCD for 4 weeks	Weltman et al., 1999
		2C11	↔	↓		NASH	MCD for 8 weeks	Lickteig, 2007
		2C39	↑			Not reported	Obese Zucker for 6 weeks	Suh et al., 2005
		2C39	↓			Not reported	Obese Zucker for 12 weeks	Suh et al., 2005
	Human	2C8	↔	↔	↔	Progression of NAFLD		Fisher et al., 2009
		2C9	↔	↔	↑	Progression of NAFLD		Fisher et al., 2009
		2C19	↔	↓	↓.	Progression of NAFLD		Fisher et al., 2009

Table 5

Table N, Effect of NAFLD on The expression and activity of X″, X being CYP1A2, CYP2E1, and CYP3A.

CYP2E1	Source	mRNA	Protein	Activity	Diagnosis	Model	Study
	Mouse	↓	↔		Steatosis	Male ob/ob at 11 weeks	Cheng et al., 2008
		↓			Steatosis	Female ob/ob at 11 weeks	Cheng et al., 2008
				↓	Not reported	ob/ob at 12 weeks	Watson et al., 1999
				↔	Not reported	ob/ob at 16 weeks	Barnett et al., 1992
			↔	↔	Not reported	Male ob/ob at 4 or 8 months	Roe et al., 1999
			↑	↑	Not reported	Female ob/ob at 4 or 8 months	Roe et al., 1999
		↓	↓	↓	Not reported	ob/ob (age not reported)	Enriquez et al., 1999
		↔	↔		Not reported	db/db at 10 weeks	Yoshinari et al., 2006
			↓		NAFLD (undifferentiated)	Intragastric overfeeding	Deng el al., 2005
			↑		Steatosis and NASH	71% fat for 8 and 16 weeks	Mantena et al., 2009
		↔			Steatosis	41% fat for 4 months	Ito et al., 2006
		↑↓*			Steatosis and NASH	60% fat for 10, 19, 34, or 50 weeks	Ito et al., 2007
			↔	↔	NASH	MCD for 31 days	Donthamsetty et al., 200
		↑	↑	↑	NASH	MCD for 10 weeks	Leclercq et al., 2000
	Rat	↓	↓	↔	Not reported	Obese Zucker (age not reported)	Enriquez et al., 1999
		↑	↑	↑	Not reported	Obese Zucker at 4 months	Khemawoot et al., 2006
		↔	↑	↑	Not reported	8.6% (w/w) fat for 3 months	Khemawoot et al., 2006
		↑			Steatosis vs NASH	35% or 71% fat for 3 weeks	Lieber et al., 2004
			↑		Not reported	65% fat for 8 weeks	Osabe et al., 2007
		↑	↑	↑	Steatosis and NASH	MCD for 4 weeks	Weltman et al., 1996
			↓		Steatosis vs NASH	Orotic acid	Zhang et al., 2007
		↑			NASH	Intragastric overfeeding	Li et al., 2011
		↑			NASH	Intragastric overfeeding	Baumgardner et al., 2008
	Human	↑			NAFLD (undifferentiated)		Kohjima et al., 2007
				↔	NAFLD (undifferentiated)		Prompila et al., 2008
		↓			NAFLD (undifferentiated)		Nakamuta et al., 2005
				↔	Steatosis		Donato et al., 2006
				↑	Steatosis		Emery et al., 2003

CYP2E1	Source	mRNA	Protein	Activity	Diagnosis	Model	Study
				↑**	Dietary restriction		Leclercq et al., 1999
			↑**		Bariatric surgery (steatosis)		Bell et al,, 2010
		↓	↓	↔	Progression of NAFLD		Fisher et al., 2009
				↔	Steatosis vs. NASH		Chtioui et al., 2007
		↑			NASH		Baker et al., 2010
			↑		NASH		Weltman et al., 1998
				↑	NASH		Chalasani et al., 2003
			↑	↑	NASH		Orellana et al., 2005
			↑	↑	NASH		Orellana et al., 2005

*Intially elevated, then decreased.

**results have been reversed, due to the nature of the study

Table 6

Table N, Effect of NAFLD on the expression and activity of X″ X being CYP1A2, CYP2E1, and CYP3A.

CYP3A	Source	mRNA	Protein	Activity	Diagnosis	Model	Study
	Mouse	↔	↓		Steatosis	Male ob/ob at 11 weeks	Cheng et al., 2008
		↓	↔		Steatosis	Female ob/ob at 11 weeks	Cheng et al., 2008
				↔	Not reported	ob/ob at 12 weeks	Watson et al., 1999
				↔	Not reported	ob/ob at 16 weeks	Barnett et al., 1992
				↔	Not reported	ob/ob at 4 or 8 months	Roe et al., 1999
		↔	↔		Not reported	db/dbatlOweeks	Yoshinari et al., 2006
		↑			Steatosis	36% fat for 12 weeks	Kim et al., 2004b
				↑	Not reported	45% fat for 6 months	Koide et al., 2010
		↓			Steatosis	60% fat for 8 weeks	Kirpich et al., 2009
		↑			NASH	MCD for 8 weeks	Fisher et al., 2008
	Rat	↑			Not reported	Obese Zucker at 6 weeks	Suh et al., 2005
		↓			Not reported	Obese Zucker at 12 weeks	Suhet al., 2005
		↓			Not reported	Obese Zucker at 14 weeks	Kim et al., 2004a
		↓			Not reported	High fat (details not reported	Hangama et al., 2007
			↓		Not reported	65% fat for 8 weeks	Osabe et al., 2007
			↓		Steatosis	Orotic acid	Zhang et al., 2007
				↓	Steatosis	MCD for 4 weeks	Weltman et al., 1996
		↑			NASH	Intragastric overfeeding	Baumgardner et al., 2008
		↑			NASH	Intragastric overfeeding	Li et al., 2011
	Human	↔	↔	↔	Progression of NAFLD		Fisher et al., 2009
			↔		NAFLD		Bell et al., 2010
				↓	Hepalocytes		Donato et al., 2006
				↓	Steatosis		Donato et al., 2007
			↓		NASH		Weltman et al., 1998

Table 7

Effect of NAFLD on the expression and activity of phase II conjugating enzymes.

UGT/SULT	Source	Diagnosis/Model	Enzyme	mRNA	Protein	Activity	Reference
	Mouse	Male ob/ob at 11 weeks	Sult2al/2	↑			Cheng et al., 2008
		Female ob/ob at 11 weeks	Sult2al/2	↔			
		ob/ob at 12 weeks	UGT			↔	Watson et al., 1999
		45% fat for 6 months	Sult2a1		↓	↓	Koide et al., 2010
			Sult1a1		↔	↔	
			Ugtla		↔	↔	
			Ugt2b		↔	↑	
		60% fat for 8 weeks	Uglta9	↓			Kirpich et al., 2009
			Ugt2bl	↓			
	Rat	Obese Zucker at 14-16 weeks	UgtlAl	↓			Kim et al., 2004a
			UgtlA6	↓			
			Ugt2Bl	↓			
		Obese Zucker at 6 months	SULT			↔	Chaudhary et al., 1993
			UGT			↑	
		65% fat for 8 weeks	UgtlAl		↓		Osabe et al., 2007
			UgtlA6		↓		
			UgtlA7		↓		
			Ugt2Bl		↓		
	Human	African Americans with NASH	SULT1A1	↓			Stepanova et al., 2010
		NASH	SULT1A2	↓			Younissi et al., 2005a

Table 8

Effect of NAFLD on glutathione content as well as gene expression and activity of related enzymes.

Glutathione	Source	Diagnosis/model	Enzyme	mRNA	Protein	Activity	Reference
	Mouse	ob/ob at 12 weeks	tGST			↔	Watson et al., 1999
			tGSH		↔		
		ob/ob at 16 weeks	tGST			↓	Barnett et al., 1992
			tGSH		↓		
		ob/ob at 17 weeks	GSTA1, A2	↑			Sharma et al., 2010
		Male ob/ob at 4 and 8 months	tGST			↓	Roe et al., 1999
		36% fat for 12 weeks	Gstm2, m6	↑			Kim et al., 2004b
			GCLC	↑			
		41% fat for 4 months	tGSH		↔		Ito et al. 2006
		45% fat for 6 monthcs	tGST				Koide et al., 2010
		59% fat for 15 weeks	Gstml	↑			Lee et al., 2010
			GSH:GSSG		↓		
		60% fat for 8 weeks	GSTA1.A2.A4	↓			Kirpich et al., 2009
			GSTM1.M3, M6	↓			
			GstPl	↓			
		60% fat for 34 and 50 weeks	tGSH		↓		Ito et al., 2007
	Rat	Obese Zucker at 14-16 weeks	GSTA2	↓			Kim et al., 2004a
		Obese Zucker at 5-6 months	tGST		↔		Chaudhary et al., 1993
			GCL		↔		
			tGSH		↔		
		MCD diet for 8 weeks	GCLC	↑			Lickteig et al., 2007
	Human	Steatosis	GSTM1.M2, M4, M	↑			Younissi et al., 2005a
		NAFLD (undifferentiated)	GSS	↔			Kohjima et al., 2007
		Steatosis and NASH	tGSH		↓		Videla et al., 2004
		NASH vs steatosis	GSTM1	↓			Yoneda et al., 2008
		NASH	GSTA4				Younissi et al., 2005b
		NASH	GSTM4, M5	↓			Rubio et al., 2007
		African American with NASH (compared to Caucasian with NASH)	GSTM2, M4, M5	↑			Stepanova et al., 2010

Glutathione	Source	Diagnosis/model	Enzyme	mRNA	Protein	Activity	Reference
		Progression of NAFLD	tGSTA		↑		Hardwick et al., 2010
			GSTA1, A2, A4	↑			
			tGSTM		↓		
			GSTM1.M3	↑			
			tGSTP		↑		
			GSTP1	↑			
			GCLC	↔	↔		
			GCLM	↑	↑		
			tGST			↓	
			GSHrGSSG		↓		

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