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The role of bile acids in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

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ABSTRACT

Nonalcoholic fatty liver disease is growing in prevalence worldwide. It is marked by the presence of macrosteatosis on liver histology but is often clinically asymptomatic. However, it can progress into nonalcoholic steatohepatitis which is a more severe form of liver disease characterized by inflammation and fibrosis. Further progression leads to cirrhosis, which predisposes patients to hepatocellular carcinoma or liver failure. The mechanism by which simple steatosis progresses to steatohepatitis is not entirely clear. However, multiple pathways have been proposed. A common link amongst many of these pathways is disruption of the homeostasis of bile acids. Other than aiding in the absorption of lipids and lipid-soluble vitamins, bile acids act as ligands. For example, they bind to farnesoid X receptor, which is critically involved in many of the pathways responsible for maintaining bile acid, glucose, and lipid homeostasis. Alterations to these pathways can lead to dysregulation of energy balance and increased inflammation and fibrosis. Repeated insults over time may be the key to development of steatohepatitis. For this reason, current drug therapies target aspects of these pathways to try to reduce and halt inflammation and fibrosis. This review will focus on the role of bile acids in these various pathways and how changes in these pathways may result in steatohepatitis. While there is no approved pharmaceutical treatment for either hepatic steatosis or steatohepatitis, this review will also touch upon the multitude of potential therapies.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is growing in prevalence worldwide. Currently, it is reported to affect about 30% of the population in the United States (Younossi et al., 2016). Yet, prevalence is likely higher than reported since NAFLD is asymptomatic and requires a tissue biopsy for diagnosis. Prevalence is also increasing in adolescents and children, with approximately 10–20% of this population affected (Temple et al., 2016). NAFLD is a spectrum of diseases ranging from simple steatosis, nonalcoholic steatohepatitis (NASH), and fibrosis. Simple steatosis can progress into NASH, which is a more severe form of liver disease marked by the presence of hepatocyte ballooning and inflammation. The prevalence of NASH in the developed world is at least 2–3% (Satapathy and Sanyal, 2015). About 30% of patients with NAFLD are estimated to develop NASH (Younossi et al., 2016). The mechanism by which this occurs is not well known. NASH can subsequently progress into liver cirrhosis and hepatocellular carcinoma (HCC). Currently, the second most common indication for liver transplants in the United States is HCC secondary to NASH but this is expected to become the number one indication in the near future (Wong et al., 2014).

Due to the growing prevalence of NAFLD, there will be an inevitable increase in the prevalence of NASH, liver cirrhosis, and HCC. Except for life style modification, no therapies exist to halt or reverse NAFLD or NASH. However, there is a lot of interest in discovering such treatments, since curing patients of NAFLD would not only prevent NASH-associated HCC, but it would also improve the multitude of comorbidities often associated with NAFLD. NAFLD and NASH often occur in conjunction with obesity, hypertension, dyslipidemia, and insulin resistance. Patients with NAFLD or NASH are also at increased risk of cardiovascular disease. Thus, understanding the mechanism behind the progression of NAFLD to NASH is crucial as this would offer some insights into potential targets for

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the development of drug therapies that can successfully reverse or halt NAFLD progression.

Bile acids (BAs) are well known for their role in fat absorption (Hofmann, 1963). However, they also act as signaling molecules involved in a variety of pathways that regulate BA, glucose, and lipid homeostasis (Patti et al., 2009; Qi et al., 2015; Watanabe et al., 2011). For this reason, pathways linked to BAs have been implicated as targets for NAFLD and NASH drug therapies. While several drugs have been developed, their success has been variable and further research still needs to be done to develop better, more reliable therapies.

2. NAFLD and NASH

Obesity predisposes individuals to the development of a fatty liver. With obesity on the rise, it is not surprising that NAFLD is becoming more prevalent. NAFLD, however, can develop in patients with normal or lean body weights. NAFLD is defined by the presence of macrovesicular fat accumulation in more than 5% of hepatocytes in patients who consume less than 20 grams of alcohol per day (Yuan and Bambha, 2015). Alterations in lipid metabolism that ultimately lead to increased fat accumulation by hepatocytes lead to steatosis.

NASH is marked by the addition of lobular inflammation and hepatic ballooning to macrovesicular fat accumulation (Ludwig et al., 1980). NASH can progress to liver fibrosis and cirrhosis. Briefly, liver fibrosis develops secondary to an imbalance in extracellular matrix (ECM) synthesis and degradation (Ebrahimi et al., 2016). Hepatic stellate cells have been implicated in this process since they are the major contributors of the deposition of ECM in the liver (Ebrahimi et al., 2016). With increasing fibrosis, the liver becomes grossly smaller, develops nodules, and liver function is compromised. Cirrhosis is characterized by irreversible hepatic scarring and is a risk factor for the development of HCC. The only potentially curative treatment for advanced, non-metastatic HCC is liver transplantation.

The exact mechanism of progression of simple steatosis to NASH is still unclear but is sure to involve a complex interplay of multiple factors and pathways among the liver, adipose tissue, and the gastrointestinal system. Multiple mechanisms have been proposed (Ebrahimi et al., 2016; Magee et al., 2016; Serviddio et al., 2016) but it is likely that progression of NAFLD is dependent on repeated hepatic insults via several different pathways (Buzzetti et al., 2016; Day and James, 1998). For example, steatosis may start with insulin resistance and obesity, which predispose to higher hepatic lipid levels. Increased lipids in the hepatocytes results in increased oxidative stress and cellular damage. Adipose tissue releases cytokines to increase inflammation and fibrosis. Gut microbiota is also believed to play a role in the development of NASH via alterations in the BA pool level and composition (Jiang et al., 2015; Liu et al., 2016b; Mei et al., 2015; Wang et al., 2016). Recently, vitamin D deficiency has been proposed as another possible factor as mice fed a high fat diet (HFD) exhibited increased steatosis and hepatic ballooning when coupled with a vitamin D deficiency (Kong et al., 2014).

There are undoubtedly numerous more pathways yet to be discovered that could help explain the link between simple steatosis and NASH, but many of the currently proposed pathways involve BAs. Total fasting and post-prandial serum BAs are increased in patients with NASH compared to patients with healthy livers (Ferslew et al., 2015). In fact, it has been proposed that patients with steatohepatitis have a shift in BA composition such that there is an increase in taurine- and glycine-conjugated BAs and increased secondary BAs (Ferslew et al., 2015; Lake et al., 2013). Another study demonstrated altered BA composition in rats fed a HFD (Suzuki et al., 2013). Secondary BAs can have harmful effects (Bartram et al., 1998; Ridlon et al., 2013) and for this reason, an increase in them may very well contribute to repeated insults of inflammation that ultimately contributes to the progression to NASH.

While NAFLD itself is asymptomatic and does not often affect liver function, it can progress into end-stage liver disease. For this reason, much research is being devoted towards finding a drug that can successfully stop NAFLD progression and, ideally, reverse its progress. To do this, a good grasp on the mechanism behind NASH development is crucial. A common factor involved with several of the pathways believed to contribute to NAFLD progression is BAs. BAs are well known for their role in lipid absorption, but they also act as ligands of various receptors to regulate BA, glucose, and lipid homeostasis. For this reason, BAs and the pathways in which they are involved are important targets for NAFLD treatments.

3. BA synthesis

BAs are amphipathic molecules synthesized from cholesterol in the liver and are a component of bile. Bile is stored in the gallbladder and upon food consumption, released into the duodenum in response to cholecystokinin (CCK), a peptide hormone synthesized in enteroendocrine cells of the duodenum. BAs aid in lipid emulsification and absorption of fat and fat-soluble vitamins.

BAs are synthesized via one of two pathways: the classical pathway (or neutral pathway) and the alternative pathway (or acidic pathway) (Zhu et al., 2016). The majority (75%) of BAs are synthesized under the classical pathway in hepatocytes (Asgharpour et al., 2015). The first step in this pathway, which is the rate-limiting step, is catalyzed by the enzyme cholesterol 7α-hydroxylase (CYP7A1) to produce 7α-hydroxycholesterol (Russell and Setchell, 1992). This enzyme is found exclusively in the liver. The BA produced via this pathway in humans is cholic acid (CA). The enzyme sterol 27-hydroxylase (CYP27A1) initiates the first step in the alternative pathway. CYP27A1 is a mitochondrial enzyme more widely distributed and found in macrophages and various tissues. The end products of this pathway include 25-hydroxycholesterol and 27-hydroxycholesterol. Chenodeoxycholic acid (CDCA) is synthesized via the alternative pathway. CA and CDCA are termed primary BAs. In mice, CDCA is further converted to muricholic acid (MCA) by Cyp2c70 and therefore the murine primary BAs are CA and MCA (Takahashi et al., 2016). The primary BAs are conjugated often with either glycine or taurine in humans or taurine in rodents, via the enzyme bile acid-CoA:amino acid N-acyltransferase (BAAT) (Johnson et al., 1991; Killenberg and Jordan, 1978). Glycine conjugation predominates over taurine conjugation in humans (Johnson et al., 1991).

4. BA transport

After BAs are synthesized, they are exported into the gallbladder and secreted into the duodenum. Most are recirculated back to the liver from the terminal ileum. The remainder enter the colon where some are reabsorbed back into the liver while others are excreted. This enterohepatic circulation of BAs involves multiple transporters (Fig. 1). These transporters are important to note since they are potential targets for therapeutic interventions. Briefly, BAs are actively transported from hepatocytes into the bile duct by canalicular BA transporters. Bile salt export pump (BSEP) is the main BA efflux transporter. Multidrug resistance-associated protein 2 (MRP2; ABCC2) belongs to the ATP binding cassette (ABC) superfamily of transporter proteins. It transports organic anions from hepatocytes into the bile duct to become a part of bile (Konig et al., 1999). As BAs are shuttled towards the gallbladder, they are