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Hepatic lipid metabolism and non-alcoholic fatty liver disease in aging

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ABSTRACT

Aging is associated with dysregulation of glucose and lipid metabolism. Various factors that contribute to the dysregulation include both modifiable (e.g. obesity, insulin resistance) and non-modifiable risk factors (age-associated physiologic changes). Although there is no linear relationship between aging and prevalence of non-alcoholic fatty liver disease, current data strongly suggests that advanced age leads to more severe histological changes and poorer clinical outcomes. Hepatic lipid accumulation could lead to significant hepatic and systemic consequences including steatohepatitis, cirrhosis, impairment of systemic glucose metabolism and metabolic syndrome, thereby contributing to age-related diseases. Insulin, leptin and adiponectin are key regulators of the various physiologic processes that regulate hepatic lipid metabolism. Recent advances have expanded our understanding in this field, highlighting the role of novel mediators such as FGF 21, and mitochondria derived peptides. In this review, we will summarize the mediators of hepatic lipid metabolism and how they are altered in aging.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in Western societies, estimated to affect up to 20% of the US adult population (Lazo et al., 2013; Younossi et al., 2016), with a much higher prevalence among obese people (Angulo, 2002). NAFLD is characterized by hepatocellular fat deposition that accounts for more than 5% of the liver weight. Although once considered a simple fat deposition (steatosis), it is now well-known that steatosis could trigger progressive pathologic changes in the liver including severe inflammation, hepatocellular ballooning, fibrotic changes and even cirrhosis (Angulo, 2002; Younossi et al., 2016). Non-alcoholic steatohepatitis (NASH) is one of the leading cause of morbidity and mortality, and is the second leading etiology among liver transplant waitlist registrants in 2013 (Wong et al., 2015). What determines the progression of steatosis to steatohepatitis remains to be fully elucidated, and is considered to be a two-hit process. It is generally accepted that fat deposition serves as the lead event, while a second hit occurring from lipotoxicity, oxidative stress and pro-inflammatory cytokines contributes to the progression to NASH (Dowman et al., 2010).

Epidemiological studies have shown an "inverted U shape" distribution in the incidence of NAFLD, incidence decreasing after 6th decade in men and 7th decade in women; however with more severe histological changes with advanced age (Bertolotti et al., 2014). Although there is no linear relationship between the prevalence of NAFLD and aging, it has been shown that aging itself enhances progression to NASH, and associated mortality (Bertolotti et al., 2014). Inflammation and oxidative stress are more pronounced with aging, explaining the more severe pathological changes in the elderly suffering from NASH. Multiple independent cohort studies have reported that NAFLD occurs at least 10 years earlier in men, and male sex is an independent risk factor (Chen et al., 2006; Xu et al., 2013; Zelber-Sagi et al., 2006). Gender-dimorphic pattern of NAFLD has led to the hypothesis that circulating estrogens provide protection in women. This is further supported by the fact that post-menopausal women on hormone replacement therapy (HRT) have better liver enzyme profile (Johnson et al., 1993). Whether the decrease in NAFLD prevalence with advanced aging is associated with HRT or modification of risk factors (e.g. obesity and insulin resistance) is difficult to answer due to lack of longitudinal data. Diet alone, likely has minimal effect on the development of steatosis given that majority of hepatic triglycerides are synthesized from non-esterified fatty acids derived

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from lipolysis of adipose tissue (Green and Hodson, 2014). Selectively increased mortality in NAFLD patients could also contribute to the observed changes in prevalence with aging (Koehler et al., 2012). Of note, NAFLD is associated with the various components of metabolic syndrome including insulin resistance, type 2 diabetes, hypertension, dyslipidemia and cardiovascular diseases (CVD) (Paschos and Paletas, 2009). Indeed, NAFLD is a strong and independent predictor for the development of metabolic syndrome, a risk for many age-related diseases (Adams et al., 2009; Alkhouri et al., 2010; Chitturi and Farrell, 2007; Fan et al., 2005; Hsiao et al., 2007; Wasada et al., 2008).

2. Physiology, regulators and changes with aging

Hepatocellular fat deposition is tightly regulated by various factors including dietary fat intake, circulating lipid levels, hepatic uptake, de novo lipid synthesis, hepatocellular lipid oxidation and export of lipids from the liver. The etiology of NAFLD is multifactorial; and results from combination of enhanced lipid delivery and uptake, increased de novo lipogenesis (DNL), changes in fatty acid oxidation (FAO) and/or decreases in hepatic lipid secretion rates (Fig. 1). To understand the factors contributing to increased risk of NAFLD and NASH with aging, we will systematically summarize the physiology and mediators of hepatic lipid metabolism, and will highlight the changes in these processes with aging.

2.1. Physiology of hepatic lipid metabolism

2.1.1. Substrate availability and transport

Substrate availability and transport directly affects hepatic lipid uptake and stores. Free fatty acids (FFAs), derived either from dietary lipids or from the adipose tissue, are taken up by the liver and utilized for energy, membrane synthesis, or stored as triglyceride (TG). FFAs enter the hepatocytes through diffusion; however transport proteins such as fatty acid transport protein (FATP) and fatty acid translocase (FAT, also known as CD36) are also important, especially for the entrance of long-chain fatty acids (LCFA; >12C) (Bazinet and Laye, 2014; Glatz et al., 2010; Goldberg et al., 2009). Under non-pathological conditions, pool of non-esterified fatty acid (NEFA) derived from white adipose tissue lipolysis is the major source for hepatic uptake, contributing up to 75% of hepatic TG depots; while the percent contribution of dietary fat is relatively small (Green and Hodson, 2014). However, the relative contribution can be altered in subjects with NAFLD, with around 60% of the liver TG arising from circulating NEFA and 15% from diet (Donnelly et al., 2005).

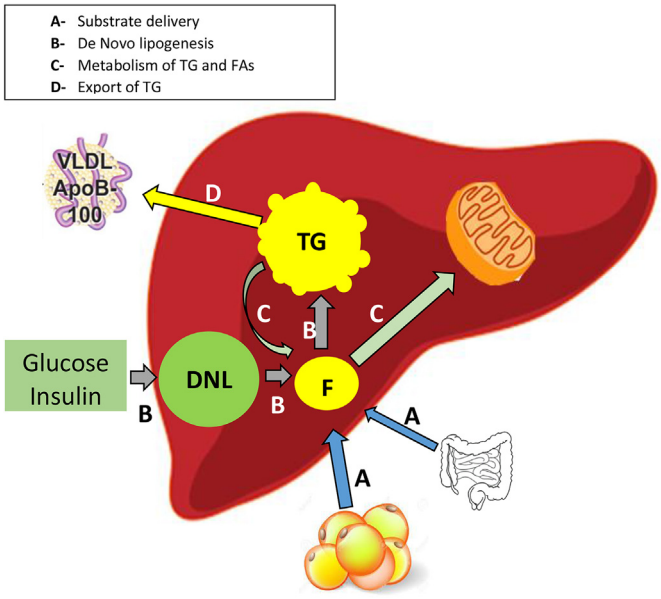

Fig. 1. Schematic view of overall hepatic lipid metabolism: Either derived from diet or obtained as a result of adipose tissue lipolysis (A), or through hepatic de novo lipogenesis (DNL) (B), fatty acids (FA) once in the liver, could be used as a substrate for fatty acid oxidation (C) or converted to triglyceride (TG) for storage and secretion (D) in the form of very-low density lipoprotein (VLDL) assembled with apolipoprotein B.

Studies have shown that increased circulating NEFA concentrations, and subsequent substrate delivery to the liver, are the key determinants of hepatic TG production. Using [U-^{13}C] palmitate to measure rates of fatty acid esterification into hepatic TG under conditions of insulin receptor knockdown, Vatner and colleagues demonstrated that delivery of fatty acid to liver is the primary determinant of hepatic TG level (Vatner et al., 2015). Aging, through increase in FFA in circulation, increases the risk for abnormal hepatic lipid accumulation; the increase in FFA is attributable to a variety of reasons including insulin resistance that is discussed in detailed in subsequent sections.

Under conditions of physiological fat intake, there is no change in absorption of fat with aging. With higher fat concentration in the diet, an increase in fecal fat was noted in old compared to young (Danford D.E., 2013). The relative fat absorption in aging is dependent on the composition of the dietary FAs, with isocaloric polyunsaturated FAs increasing lipid absorption and weight gain (Woudstra et al., 2004a). Though some studies have shown changes in absorptive capacity of the small intestine, and potentially decreased or delayed absorption of fatty acids from the diet (Woudstra et al., 2004b), most of the studies demonstrate that the contribution of changes in dietary fat absorption to the development of hepatic steatosis is probably minimal in healthy aging (Ferramosca and Zara, 2014; Holt and Balint, 1993).

Once taken up by the hepatocytes, binding of FFA to fatty acid binding protein (FABP)-1 (also known as Liver-FABP or L-FABP), directs FFAs from cytoplasm to different compartments within the cell either for metabolism or for regulation of gene expression through interaction with transcription factors, such as peroxisome proliferator-activated receptor (PPAR)α (Chen et al., 1986), thereby protecting liver from lipotoxicity (Fig. 2). Level of FABP1 decreases in Fischer rats with age (Woudstra et al., 2004b). FABP1 level are also decreased in NAFLD and genetic lipid disorders such as abetalipoproteinemia and Anderson's disease (Wang et al., 2015). The reduction in FABP1 with aging and in NAFLD causes impairment in β-oxidation through changes in PPARα, thereby exacerbating the potential lipotoxicity, and contributing to the pathogenesis and progression of NAFLD. Indeed, Nanji et al. showed that the severity of fatty liver was negatively correlated with the level of FABP1 in rodents (Nanji et al., 2004). Though the data on LFABP -/- mouse phenotype are conflicting in terms of total body weight and adiposity, a decrease in hepatic long chain fatty acid (LCFA) uptake/oxidation and reduction in hepatic steatosis have been reported (Atshaves et al., 2010; Newberry et al., 2012). Restoration of FABP1 levels with fish oil treatment has been shown to improve systemic metabolic profile and markers of inflammation in diabetic rats, while PPARα agonist has been shown to decrease oxidative stress, inflammation and steatosis and in models of ethanol induced stress (Nanji et al., 2004). In a study of 372 Chinese adults, serum FABP1 correlated with obesity, insulin resistance, hypertriglyceridemia and low HDL-cholesterol (Shi et al., 2012). These findings suggest a key role for FABP1 not only in hepatic lipid metabolism but also hepatic cytoprotection; therefore FABP1 is an important target for drug discovery to prevent oxidative stress- and lipotoxicity-induced hepatic damage.