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Minireview

Nonalcoholic fatty liver disease: Current and potential therapies

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver injury worldwide. It covers a wide spectrum of hepatic disorders ranging from simple steatosis, through steatohepatitis (steatosis with inflammation), to cirrhosis. The molecular and cellular mechanisms underlying hepatic injury in NAFLD are not clear. Several evidences suggest that multiple mechanisms including insulin resistance, oxidative stress, inflammation, and genetic factors interact to initiate the development of NAFLD. Despite that there is currently no approved drug therapy for NAFLD, many approaches appear to be beneficial. Insulin sensitizers, antioxidants and antiinflammatory agents showed promising effects. This review highlights the current as well as the potential therapies of NAFLD.

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Contents

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Introduction

Nonalcoholic fatty liver disease (NAFLD), first described in 1981, is a term that represents a spectrum of hepatic disorders ranging from simple triglyceride (TG) accumulation in hepatocytes (hepatic steatosis) through hepatic steatosis with inflammation (steatohepatitis) commonly known as nonalcoholic steatohepatitis (NASH), to cirrhosis (Farrell and Larter, 2006). By definition, NAFLD is seen in people whose daily alcohol intake is less than 10 g for women and less than 20 g for men. NAFLD affects 10–24% of the general population in various countries. The prevalence of NAFLD rises to 57.5–74% in obese persons. It affects 2.6% of children, and 22.5–58.5% of obese children (Tarantino et al., 2007). In NAFLD cirrhosis, 30% to 40% of patients will experience a liver-related death (McCullough, 2006). Currently, there is no satisfying therapeutic strategy for NAFLD. This review highlights the available as well as the potential therapies of NAFLD.

Molecular mediators of NAFLD

Understanding the pathophysiology of NAFLD is extremely important to develop sound therapeutic interventions. Despite the exact pathology underlying NAFLD is unknown, there is an accepted concept for the pathophysiology of NAFLD that is called "multiple hit" hypothesis (McCullough, 2006). According to this hypothesis, multiple factors interact for the development of NAFLD (Fig. 1). The first hit is the accumulation of fat in hepatocytes mostly due to insulin resistance (IR) (Chitturi et al., 2002). The subsequent hits involve a combination of oxidative stress, lipid peroxidation, and release of inflammatory mediators (Anstee and Goldin, 2006). Additionally, genetic and immune factors are involved in the initiation and progression of NAFLD (Kotronen et al., 2009). Moreover, it has become evident that obesity, dyslipidemia, diabetes, and hypertension, are key risk factors for the development and progression of NAFLD (Targher et al., 2005).

Insulin resistance

Insulin resistance (IR) is defined as decreased insulin mediated uptake of glucose in tissues such as skeletal muscle and adipocytes. The degree of IR has been correlated with the severity of NAFLD (Bugianesi et al., 2004). Peripheral IR leads to an influx of free fatty acids (FFAs) to the liver both by decreased suppression of lipolysis and increased de novo lipogenesis in the liver. The subsequent accumulation of fat within the hepatocytes leads to the development of hepatic IR (Kim et al., 2001). In IR, the combination of elevated plasma concentrations of glucose and fatty acids promotes hepatic fatty acid synthesis and impairs β-oxidation leading to hepatic steatosis (Sanyal et al., 2001). An important mechanism of IR is downregulation of insulin receptor substrate 1 (IRS-1) signaling by excess FFAs that impair the tyrosine phosphorylation of IRS-1 (Dey et al., 2005). Insulin sensitivity is also regulated by peptide mediators. Adipose tissue, especially mesenteric fat with its venous blood flowing directly to the liver, is a rich source of cytokine and peptide hormone production that regulates downstream metabolic activity. Examples include tumor necrosis factor-α (TNF-α), angiotensinogen, plasminogen activator inhibitor-1, leptin, and complement components (Tarantino et al., 2007). It has been reported that hepatic steatosis leads to hepatic IR by stimulating gluconeogenesis and activating protein kinase C (PKC) and Jun N-terminal kinase, which may interfere with tyrosine phosphorylation of IRS-1 and IRS-2 and impair the ability of insulin to activate glycogen synthase (Samuel et al., 2004).

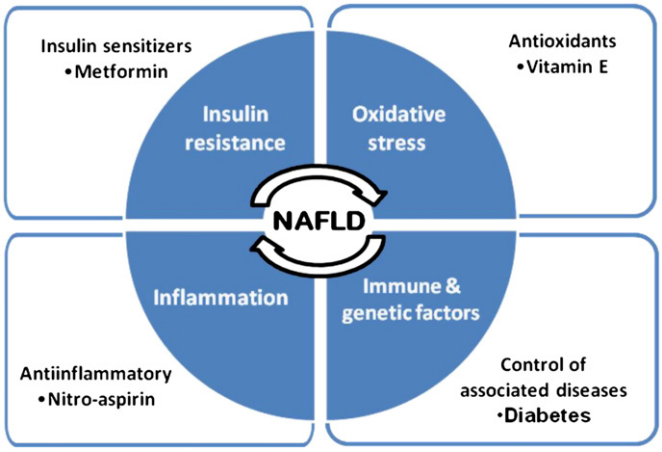

Fig. 1. Pathogenesis and potential therapy of nonalcoholic fatty liver disease (NAFLD). Development of NAFLD is due to interaction between multiple factors mainly; insulin resistance, oxidative stress, inflammation and genetic predisposition. The potential therapies of NAFLD target one or more of these factors.

Oxidative stress/mitochondrial dysfunction

Oxidative stress occurs as a result of either excess generation of reactive oxygen species (ROS) within the hepatocyte or reduced antioxidant defences. In the liver, oxidative stress results in activation of hepatic stellate cells as well as accumulation of fat within hepatocytes. Oxidative stress not only results in the generation of ROS, but also enhances peroxisomal and mitochondrial β-oxidation. Peroxisomal β-oxidation results in the generation of acyl-coenzyme A, which if left unmetabolized, functions as peroxisome proliferator activator receptor-alpha (PPAR-α) ligand (McAvoy et al., 2006).

PPAR-α receptor plays a vital role for hepatocytes to sense excess FFAs (Ip et al., 2004). Normal activation of PPAR-α receptor by synthetic or natural PPAR-α ligands upregulates transcriptional genes responsible for fatty acid oxidation (Seo et al., 2008). Animals deficient for the Acyl-COA oxidase 1 (ACOX1) have high levels of the very long chain fatty acids that are incapable of entering the fatty acid oxidation pathway due to ACOX1 deficiency. These unmetabolized substrates hyperactivate PPAR-α causing lipotoxicity characterized by increased oxidative-stress and lipid peroxidation, thus promoting the progression of simple hepatic steatosis to steatohepatitis (Peraza et al., 2006).

Inflammation/adipocytokines

Adipose tissue secretes a number of physiologically active peptides. These peptides or "adipocytokines" can be classified as proinflammatory, such as leptin, TNF-α and interleukin-6 (IL-6), or antiinflammatory and anti-steatotic, such as adiponectin. They all have a role in the regulation of adipocyte metabolism, with a direct role in several insulin-mediated processes (McAvoy et al., 2006). A role of TNF-α in the link between adipose tissue mass and IR has been reported (Lofgren et al., 2000).

Immune response

Alterations in immune response have been implicated in the pathogenesis of NAFLD. NAFLD is associated with increased levels of the proinflammatory T helper 1-associated cytokines TNF-α and interleukin-12 (IL-12). In NAFLD loss or depletion of hepatic natural killer T (NKT) cells was reported. NKT cells and Kupffer cell-derived IL-12 may have a regulatory role during pathogenesis of NAFLD (Kremer et al., 2010).

Genetic factors

Valenti et al. examined TNF-α polymorphisms and concluded that these may also represent a susceptibility genotype for IR and NAFLD. It is however regarded that IR in patients with NAFLD is a result of multiple gene polymorphisms interacting with environmental

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