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Ezetimibe as a potential treatment for non-alcoholic fatty liver disease: is the intestine a modulator of hepatic insulin sensitivity and hepatic fat accumulation?

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Non-alcoholic fatty liver disease (NAFLD) is the hepatic component of the metabolic syndrome and is known to be associated with marked insulin resistance and increased risk of cardiovascular disease. Ezetimibe, an inhibitor of intestinal cholesterol absorption, inhibits Niemann-Pick C1-like 1 (NPC1L1). Interestingly, NPC1L1 is abundantly expressed in human liver, as well as in the intestine. Recent reports suggest a potential benefit of ezetimibe in improving hepatic insulin sensitivity and decreasing hepatic inflammation and lipid accumulation. Insulin resistance and excess hepatic fat accumulation are regarded as key factors in the pathogenesis of NAFLD. We suggest, therefore, that urgent studies are needed to assess the potential therapeutic benefit of ezetimibe in treating NAFLD.

Introduction

Ezetimibe inhibits intestinal uptake of cholesterol and is used in clinical practice to lower low-density lipoprotein cholesterol. The major metabolic pathway for ezetimibe consists of glucuronidation of the 4-hydroxyphenyl group by uridine 5′-diphosphate-glucuronosyltransferase isoenzymes to form ezetimibe-glucuronide in the intestine and liver. Approximately 78% of the ezetimibe dose is excreted in the faeces as ezetimibe, and the remainder is excreted in the urine, mainly as ezetimibe-glucuronide [1]. Niemann-Pick C1-like 1 (NPC1L1) is highly expressed in jejunum of different species and in human liver. In the intestine, NPC1L1 is the main transporter of intestinal cholesterol. Mice deficient in NPC1L1 show a marked reduction in cholesterol absorption (>70%) without a decrease in plasma with ezetimibe treatment, leading to the conclusion that ezetimibe reduces intestinal absorption via inhibition of the action of NPC1L1 [2] (Fig. 1).

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver diseases associated with fatty infiltration in hepatocytes (steatosis). Once hepatic steatosis is established, other factors – including oxidative stress, mitochondrial dysfunction and inflammation – can promote further cellular damage and might lead to non-alcoholic steatohepatitis (NASH), increasing fibrosis and cirrhosis. Major risk factors for NAFLD are obesity and insulin resistance, and, to date, the only effective treatment for NAFLD is weight loss with attention to lifestyle, which is difficult to achieve for most NAFLD patients [3]. In this article, our focus is the theoretical benefit of ezetimibe use in the treatment of NAFLD.

Ezetimibe and NAFLD

Recent evidence suggests that ezetimibe has a beneficial effect in the treatment of NAFLD. Zheng *et al.* [4] have shown that ezetimibe treatment for four weeks reduced alanine aminotransferase (ALT), hepatic triglyceride (TG), hepatomegaly, cholesterol ester and free cholesterol in diet-induced obese mice fed a high-fat and high-cholesterol diet for seven months. Importantly, administration of ezetimibe in obese Zucker rats (a model of NAFLD and metabolic syndrome) produced a marked improvement in plasma cholesterol and TG

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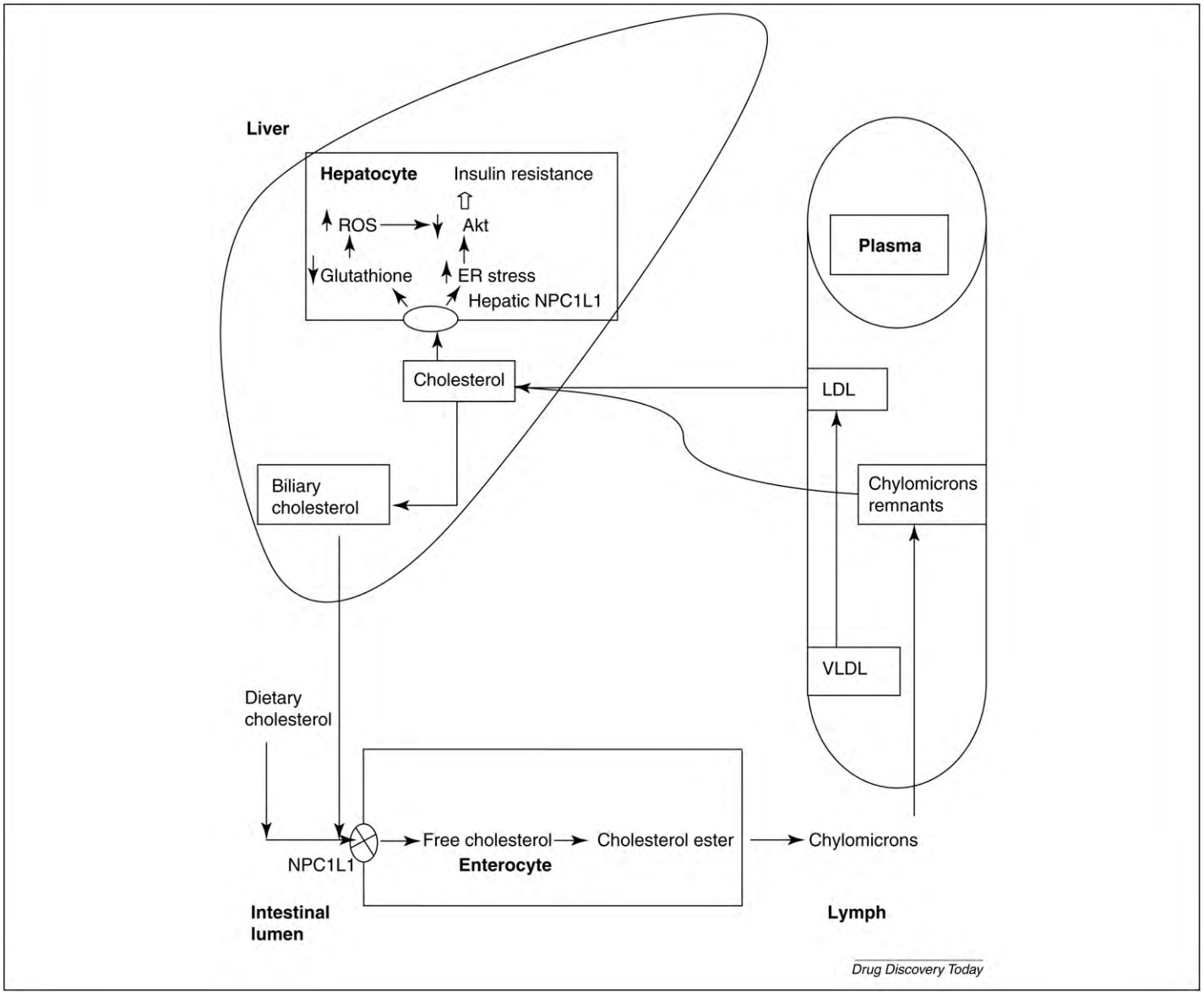

FIGURE 1

Illustration showing actions of ezetimibe treatment in the intestine and liver, suggesting that ezetimibe might be a potential treatment for insulin resistance. Abbreviations: ES, endoplasmic reticulum stress, ROS, reactive oxygen species.

levels and hepatic steatosis and improved insulin sensitivity [5]. These data are in accordance with a recent study by Nomura *et al.* [6], which showed that ezetimibe improved hepatic insulin sensitivity in obese Zucker fatty rat. Hughes *et al.* [7] have also demonstrated in human that administration of ezetimibe in six patients with ultrasound evidence of NAFLD resulted in the normalization of ALT. Administration of ezetimibe for six months in non-obese patients with NAFLD has resulted in normalization of the ALT [8]. Importantly, administration of ezetimibe with moderate weight loss in 15 patients with fatty liver for 16 weeks was associated with improvement of hepatic steatosis, inflammation and LDL-apoB100 metabolism [9], and administration of ezetimibe for six months in patients with NASH and dyslipidaemia was associated with marked histological improvement of NASH score [10]. Furthermore, administration of ezetimibe with other lipid-lowering, glucose-lowering or insulin-sensitizing agents has resulted in a marked improvement in NAFLD. For example, administration of ezetimibe with the alpha-glucosidase inhibitor acarbose for 24 weeks improved histological findings in a mouse model of NAFLD [11]. In addition, administration of a combination of valsartan, metformin and rosiglitazone for a total of 15 weeks in a rat model of NAFLD produced a marked decrease in liver steatosis (−54%), hepatic TG (−64%), hepatic cholesterol (−31%) and hepatic MDA (−70%; MDA is widely used as an indicator of free-radical-mediated lipid peroxidation injury) [12]. Interestingly, the administration of ezetimibe and simvastatin for six months in 19 people with type 2 diabetes and NAFLD was associated with a marked improvement in liver enzymes (ALT and aspartate aminotransferase) [13]. Because statins have no therapeutic or toxic effect in NAFLD, it is likely that ezetimibe treatment *per se* has the potential to reduce hepatic lipid accumulation. Moreover, the data discussed above suggest that ezetimibe improves hepatic insulin sensitivity; hepatic insulin resistance and hepatic fat accumulation are two key factors occurring early in the pathogenesis of NAFLD.

Ezetimibe and insulin resistance

Ezetimibe treatment for 24 weeks in a rat model of NAFLD was associated with a marked decrease