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IL-6 in non-alcoholic fatty liver disease – good, evil or both?

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Introduction

The role of IL-6 in non-alcoholic fatty liver disease (NAFLD) which is closely associated with obesity and insulin resistance remains controversial [1,2]. Hepatic steatosis which renders the liver more susceptible to progressive liver diseases like non-alcoholic steatohepatitis (NASH) and liver cirrhosis is detected in about 50% to 60% of obese subjects. Prevalence in the general population is 20% to 30% [1]. IL-6 is a cytokine with pleiotropic functions and systemic levels are consistently increased in obesity, a state of low grade chronic inflammation [1,3,4]. In overweight and obese subjects systemic IL-6, adipose-tissue released IL-6 and monocyte IL-6 synthesis are induced [3,5,6]. Systemic concentrations of IL-6 are about 1 pg/ml in resting, healthy controls and are about 2 to 4 fold higher in obesity [5]. Hypertrophic adipose tissue produces increased levels of IL-6 and about one third of plasma IL-6 is derived from fat tissue where it is mainly released by non-adipocytes [7]. Inflammatory cytokines interfere with insulin signalling and various *in vitro* and *in vivo* studies demonstrate that IL-6 is capable of inducing liver insulin resistance which is a major contributor to fasting hyperglycemia. IL-6 increases gluconeogenesis in primary cultures of rat hepatocytes and rat hepatoma cells [8,9]and the hepatic expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) is induced in mice by injection of IL-6 [8,10,11]. Whereas fasting glucose is similar in IL-6 knockout mice compared to wild-type animals blood glucose is mildly increased in the non-fasting state [9]. Injection of IL-6-neutralizing antibodies in ob/ob mice markedly enhances insulin-mediated suppression of endogenous glucose production when determined by hyperinsulinemic-euglycemic clamp technique [10]. Neutralization of IL-6 further improves insulin sensitivity determined by 2 h insulin tolerance tests [10]. Sabio et al demonstrated that c-Jun NH_2-terminal kinase 1 (JNK1) activation in adipocytes enhances IL-6 release which subsequently causes hepatic insulin resistance partly by upregulation of suppressor of cytokine signalling 3 (SOCS3) in the liver [11].

Synthesis of IL-6 in visceral fat exceeds production in subcutaneous fat and IL-6 in portal vein is about 20% to 30% higher compared to hepatic vein blood and systemic levels [12,13]. IL-6 in the portal vein of morbidly obese patients positively correlates with systemic C-reactive protein (CRP) an established marker of inflammation [12]. Visceral adiposity bears a higher risk to develop NAFLD [1,14]. One possible explanation is that metabolites / cytokines etc. from splanchnic organs including visceral fat depots have to pass the liver and thereby may affect hepatocyte function [12,13,15]. This hypothesis is supported by a recently published study. Transplantation of epididymal fat pads of mice into littermates to the parietal peritoneum with caval/systemic venous drainage has no effect on hepatic insulin sensitivity. Transplantation to the mesenterium which confers portal venous drainage impairs liver insulin sensitivity. Here, portal vein but not systemic IL-6 is increased. Interestingly when mice receive portal drained transplants from IL-6 knockout animal's glucose tolerance is not impaired [16].

Weight loss and regular physical exercise may reduce ectopic fat storage and can even improve NASH [17]. Contracting skeletal muscle releases IL-6 and plasma IL-6 rises by a factor of 10 to 100-fold ranging from 10 to 100 pg/ml [18]. This increase is proportional to exercise duration, intensity, muscle mass involved and endurance capacity [19]. IL-6 peak levels are reached at the end of exercise and then rapidly decline. Muscle derived IL-6 is suggested to enhance hepatic glucose release to provide additional energy [18-20]. However, plasma glucose is relatively stable and uptake of glucose by skeletal muscle may prevent hyperglycemia. Regular training is associated with lower systemic IL-6 levels at rest [18,19].

IL-6 binds to the IL-6 receptor thereby inducing homodimerization of glycoprotein 130 (gp130) and formation of a functional receptor complex of IL-6, IL-6 receptor and gp130 [18,21]. IL-6 signalling involves the Janus kinase – signal transducer and activator of transcription 3 (JAK – STAT3) pathway. In contrast to data referred to above showing that IL-6 increases hepatocyte glucose synthesis, activation of STAT3 is linked to the suppression of gluconeogenic genes in the liver. Here, IL-6 is shown to downregulate glucose-6-phosphatase (G6Pase) by STAT3 dependent pathways [22].

Recent findings even indicate that IL-6 mediates the insulin sensitizing effects of adiponectin. Adiponectin is mainly released by adipocytes and low levels in obesity are suggested to contribute to impaired glucose homeostasis and NAFLD [1,23]. Adiponectin induces IL-6 synthesis in monocytes and macrophages [24-27]. In mice injection of adiponectin transiently increases IL-6 synthesis in adipose tissue macrophages and plasma IL-6 is about 6 to 8-fold elevated. Hepatic STAT3 becomes activated and upregulates insulin receptor substrate-2 (IRS-2) in the liver and thereby may enhance hepatic insulin activity [25]. In steatotic liver of ob/ob mice with increased circulating IL-6, however, hepatic IRS-2 is reduced and contributes to hepatic insulin resistance [28,29]. This indicates that hepatic insulin sensitivity is enhanced by transient, high grade elevation of IL-6 but not by low grade chronically increased IL-6. Nevertheless, long-term rise of human IL-6 in IL-6 transgenic mice also revealed that animals become more insulin sensitive when kept on normal and high fat diets [30]. Mice where IL-6 receptor has been specifically ablated in liver parenchymal cells have increased hepatic inflammation and impaired hepatic and peripheral insulin sensitivity [31]. When IL-6 deficient mice are kept on a high fat diet hepatic insulin resistance becomes worse and inflammation develops [32].

Choline deficient diets increase liver fat content because release of triglyceride rich lipoproteins is impaired. Animals kept on this diet have hepatic inflammation and fibrosis, and therefore, this model is used to study NASH [33]. It has been shown that IL-6 improves lipid disturbances in hepatocytes isolated from these animals [34]. IL-6

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injection also lowers steatosis by increasing triglyceride release. In isolated rat hepatocytes IL-6 also stimulates hepatic triglyceride release which may contribute to reduce liver steatosis but also promotes hypertriglyceridemia [35]. Serum aminotransferase concentrations as a marker of hepatocyte injury are reduced upon IL-6 application in ob/ob mice as well as in diet-induced obese mice [36]. Here, it has to be considered that IL-6 has a very short half-life [18]suggesting that serum IL-6 is only transiently increased when injected.

IL-6 knock-out mice fed a choline-deficient, ethionine-supplemented diet more quickly develop liver steatosis and hepatocyte injury. Mice where gp130 has been knocked-out in hepatocytes have steatosis, inflammation and early fibrosis [37]. When db/db mice are fed a methionine choline deficient diet hepatic IL-6 receptor and gp130 mRNA expression are reduced. IL-6 receptor neutralizing antibody further lower expression of STAT3 regulated antiapoptotic genes and increase oxidative stress, hepatocyte apoptosis and liver fibrosis [38].

Systemic IL-6 is increased in obesity, and weight loss as well as regular exercise are associated with reduced resting serum levels [6,39,40]. While some of the data mentioned above suggest that higher IL-6 may contribute to inflammation and eventually insulin resistance it may also be speculated that IL-6 is increased because of IL-6 resistance. Indeed it is hard to believe that the modest, 2- to 3-fold increase of IL-6 in obesity may have harmful physiological consequences. One major concern of the in-vivo and in-vitro experiments analysing IL-6 effects is that the concentrations used are up to 1000 fold higher than levels measured in serum. Therefore, studies using physiological IL-6 concentrations may help to resolve the role of IL-6 in obesity and associated liver disease. The findings that IL-6 is transiently increased during physical activity and by adiponectin injection argue against injurious effects of this cytokine in obesity [18,25,41]. Exercise can elevate systemic IL-6 10 to 100-fold and adiponectin injection in mice increases IL-6 in serum at least 8-fold [18,25,41]. Nevertheless, it can not be completely ruled out that low grade chronic and high grade acute increase of IL-6 have contrary effects. Source of IL-6 may also have an effect and higher levels in portal vein have been shown to contribute to systemic inflammation and liver injury independent of serum IL-6 [12,16]. IL-6 activity is also influenced by other signalling pathways, cytokines and hormones [42-44] and this further complicates interpretation of experimental results. In summary the physiological function of IL-6 in metabolic liver disease is still not well understood. Whether its effects are good or evil seems to depend on the site and the time of production, and the metabolic context.

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