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Review

Glucocorticoids and non-alcoholic fatty liver disease

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the global obesity and metabolic disease epidemic and is rapidly becoming the leading cause of liver cirrhosis and indication for liver transplantation worldwide. The hallmark pathological finding in NAFLD is excess lipid accumulation within hepatocytes, but it is a spectrum of disease ranging from benign hepatic steatosis to steatohepatitis through to fibrosis, cirrhosis and risk of hepatocellular carcinoma. The exact pathophysiology remains unclear with a multi-hit hypothesis generally accepted as being required for inflammation and fibrosis to develop after initial steatosis. Glucocorticoids have been implicated in the pathogenesis of NAFLD across all stages. They have a diverse array of metabolic functions that have the potential to drive NAFLD acting on both liver and adipose tissue. In the fasting state, they are able to mobilize lipid, increasing fatty acid delivery and in the fed state can promote lipid accumulation. Their action is controlled at multiple levels and in this review will outline the evidence base for the role of GCs in the pathogenesis of NAFLD from cell systems, rodent models and clinical studies and describe interventional strategies that have been employed to modulate glucocorticoid action as a potential therapeutic strategy.

Contents

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1. Non-alcoholic fatty liver disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is the most common liver abnormality in the western world. It is tightly associated with obesity, metabolic syndrome and type 2 diabetes [1–4] and is rapidly becoming the leading cause of liver failure and need for transplantation [5]. The hallmark pathological finding is one of excess triglyceride (TAG) accumulation within hepatocytes (steatosis) [6]. It is a spectrum of disease that has the potential to progress from simple lipid accumulation (that is widely believed to have a benign prognosis) through to inflammation (non-alcoholic steatohepatitis, NASH) [7] with the potential for scarring, fibrosis and cirrhosis with a significant increased risk of hepatocellular carcinoma [8]. NAFLD remains a diagnosis of exclusion that can only be made in the absence of excess alcohol consumption or other pathological aetiology [9]. Data on its prevalence vary according to diagnostic criteria, the specific tests used and the population under investigation. Approximately 30% of adults in unselected populations have hepatic steatosis [10] and in those patients undergoing bariatric surgery, nearly all (>90%) will have hepatic steatosis at the time of surgery [11]. An important consideration is that whilst non-invasive assessments are able to provide accurate measurements of liver fat, the gold standard for accurate staging of disease (including inflammation and fibrosis) remains liver biopsy.

A complete understanding of the molecular mechanisms that underpin the pathogenesis of NALFD has proved elusive [12]. *In vitro* and animal models have provided significant mechanistic insight and 'multi-hit' models have been proposed that include propensity to lipid accumulation, triggers to inflammation and fibrosis and impaired liver regenerative capacity. 'Organ crosstalk' between adipose and liver tissues is also important in the development of NAFLD/NASH [1,13]. Given the proximity of visceral adipose tissue to the liver and the anatomy of the portal circulation, visceral adipose tissue directly impacts on liver function (and hepatic steatosis). Non Esterified Fatty Acids (NEFAs) and adipokines secreted from visceral adipose tissue pass directly to the liver 1st before entering the peripheral circulation. Up to 60% of liver fat content in NAFLD comes from NEFAs generated from adipose tissue [14]. The liver however, is not simply a target for delivery of circulating free fatty acids, it can also autonomously generate lipid via *de novo* lipogenesis (DNL). Hepatic DNL converts carbohydrate to fatty acids via the pre-cursor malonyl CoA and hepatocytes can then generate triglyceride by combining free fatty acids with glycerol (esterification) [15]. Cholesterol esters are also generated by hepatocytes and either stored as lipid droplets or released into the circulation as Very Low Density lipoprotein (VLDL).

Glucocorticoids (GC) have the potential to drive and modulate these processes and have therefore been implicated in the pathogenesis of NAFLD. Importantly, patients with GC excess (Cushing's syndrome), develop hepatic steatosis as well as obesity and insulin resistance in a significant proportion of cases [16]. In this review we will outline the current evidence highlighting the role of GCs and their pre-receptor metabolism in the pathogenesis of NALFD from human and animal models and *in vitro* studies. We will focus on both tissue effects and the pre-receptor metabolism of GCs affecting liver (and adipose) tissue and causing NAFLD.

1.1. Glucocorticoid action

Cortisol is the principle GC in humans (corticosterone in rodents) and circulating levels are controlled by the Hypothalamic Pituitary Adrenal (HPA) axis. The anterior pituitary secretes Adrenocorticotrophin Hormone (ACTH), which stimulates adrenal cortisol production in a diurnal pattern. Tissue cortisol concentrations are controlled by a series of enzymes that regenerate and deactivate GCs (tissue GC metabolism). These include 11β-Hydroxysteroid Dehydrogenases (11β-HSD1 + 11β-HSD2) and A-ring reductases (5α + 5β reductase). The liver itself has been shown to produce significant amounts of cortisol into the splanchnic circulation [17]. The effects of GCs are mediated via the glucocorticoid receptor (GR), which is a member of the steroid hormone receptor superfamily [18,19]. Prolonged and excessive exposure to GCs with activation of the GR can have detrimental consequences including NAFLD [20]. Dysregulated activity of 11β-HSD1 and 5αR have also been implicated in NAFLD and inflammatory metabolic disease [21–25]. It has been hypothesised that in the early phase of NAFLD with simple steatosis, liver exposure to GC may be reduced with enhanced GC clearance predominating as a protective mechanism [25]. The pathophysiology of steatohepatitis developing from simple steatosis remains unclear, although alterations in cytokines including TNFα, IL6 and MCP1 as well as NEFAs are believed to be involved in chronic inflammation and immune cell activation [26]. However, a 'switch' in GC metabolism also occurs in the inflammatory part of the condition (NASH) whereby liver exposure to GCs increases due to increased tissue regeneration. In the inflammatory component, macrophages have increased expression of 11β-HSD1 and overall, increased local GC regeneration and action represents a protective, local anti-inflammatory response.

In addition to their potent anti-inflammatory actions, GCs are key regulators of carbohydrate and lipid metabolism and energy balance [27,28]. GCs are traditionally regarded as 'flight and fight' hormones and in the fasted state they have a fundamental role to mobilize fuel for ATP generation, driving gluconeogenesis, glycogenolysis and lipolysis [27]. However, in the fed state in the presence of insulin, they can have fundamental differing actions acting synergistically with insulin [29]. Furthermore, GCs can act in a tissue specific manner and therefore they have the potential to modify metabolic phenotype in both liver and adipose tissue [30]. The majority of data linking GCs and the development of NAFLD come from *in vitro* and rodent models however there is a growing body of evidence from clinical, translational studies [21,31].

1.2. Glucocorticoids and NAFLD (liver tissue)

1.2.1. In vitro *data*

GCs drive the availability of glucose as a substrate for De Novo Lipogenesis (DNL) by stimulating gluconeogenesis in the liver and promoting glycogenolysis [32]. GCs promote insulin induced lipogenesis in rat hepatocytes [33,34]. GCs In hepatocytes, are potent regulators of key genes that drive lipogenesis including fatty acid synthase (FASN) and acetyl-CoA carboxylases 1 and 2 [35], stimulating DNL and free fatty acid utilisation and promoting hepatic steatosis [36,37]. GCs also regulate cholesterol and fatty acid synthesis [38] and HDL processing in hepatocytes [39], which can contribute significantly to lipid accumulation and reduced VLDL secretion. In rat hepatocytes, dexamethasone up-regulates HDL binding sites [39] and dexamethasone (with insulin) regulates apolipoprotein gene expression [40,41]. Whilst some studies have shown that GCs alone can increase lipid accumulation in hepatocytes [42,43] others have demonstrated a synergistic relationship with insulin to promote lipid accumulation through increased synthesis and decreased secretion [33,44]. Studies in rodent cells have been endorsed using human models. In human foetal hepatocytes, GCs increase cholesterol synthesis in a dose-dependant manner [45].

1.2.2. In vivo *animal models*

There is no doubt that *in vivo* rodent models have enhanced our understanding of the role of GCs in the pathogenesis of NAFLD.