Glucocorticoids and Non-Alcoholic Fatty Liver Disease.

Conor P Woods, Jonathon M Hazlehurst, Jeremy W Tomlinson.

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Address for correspondence:

Professor Jeremy W Tomlinson PhD FRCP
Oxford Centre for Diabetes Endocrinology & Metabolism (OCDEM),
Churchill Hospital,
Headington,
Oxford,
OX3 7LJ,
UK.

E-mail. Jeremy.tomlinson@ocdem.ox.ac.uk
Tel. +44 1865 857359

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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.

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.

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 pre-dominating 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).

Glucocorticoids and NAFLD (Liver tissue).

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).

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. Rodents treated with corticosterone develop hepatic steatosis (30,46). In combination with a high fat diet, GC excess was associated with increased fibrosis although interestingly the inflammatory response was relatively suppressed (46). GCs increase lipid biosynthesis within the liver that can lead to hepatic steatosis as well as increasing circulating TAG levels (47,48). Multiple mechanisms are believed to be important including, increased hepatic Diaglyceride Acyltransferase (DGAT) expression (37) and enhanced free fatty acid delivery into the portal circulation

Alterations in lipid utilization (as opposed to synthesis) contribute less to hepatic lipid accumulation overall. However, GCs have been shown to regulate these processes. GCs can also increase TAG hydrolysis by activating key enzymes such as PNPLA2 (35) as well as inducing specific microRNAs that have the potential to modulate lipid homeostasis (49). Dexamethasone inhibits mitochondrial matrix acyl-CoA dehydrogenases (matrix located medium and short chain) and fatty acid β-oxidation (50). CD36 is a lipid transporter molecule that has a crucial role in fatty acid uptake into

tissues (51). Several studies have demonstrated increased CD36 expression following GC treatment and this offers an additional potential driver to lipid accumulation within the liver (30).

In humans, GCs are prescribed widely (52) for a variety of medical conditions and their use is associated with an adverse metabolic profile including NAFLD, obesity, hypertension, insulin resistance, proximal myopathy, increased fracture risk, skin thinning and bruising, collectively termed, Cushing's syndrome (31,53,54). The mechanisms that contribute to GC-induced NAFLD have not been explored in detail in clinical studies. In a single small study examining patients with Cushing's syndrome, computerised tomography showed NAFLD present in 20% of patients (16). Conversely in people with NAFLD, increased circulating GC levels have been suggested to be an important driver of the disease. In 50 patients with type 2 Diabetes and NAFLD, Targher et al demonstrated sub-clinical hypercortisolism (elevated urinary free cortisol measurements and higher 9.0am cortisol following over night 1mg dexamethasone suppression), in comparison with matched controls without NAFLD (55). Evidence for activation of the HPA axis in other clinical studies within patients with NAFLD has also been postulated (56) Although in larger epidemiological studies circulating cortisol levels show no association with NAFLD (57). Indeed, in obesity, a condition with high prevalence of NALFD, circulating cortisol levels are normal or low in comparison with lean controls (58) This inconsistency and lack of association between circulating cortisol levels and NAFLD may suggest a more tissue specific role of GCs and their metabolism in the pathogenesis of NAFLD.

Glucocorticoids and NAFLD (Adipose tissue).

GC action in adipose tissue is also a key driver in the pathogenesis of NAFLD. In rodent adipocytes, GCs increase fatty acid release through increased expression of hormone sensitive lipase (HSL) (59). GCs increase expression of ATGL (desnutrin) that is also crucial in hydrolysing TAG (30,60). In addition, in the absence of insulin, GCs decrease lipogenesis through decreased ACC activity (29), and therefore in the fasting state through a

combination of increased lipid mobilization and decreased storage in adipose tissue, there will be enhanced delivery of fatty acid to the liver that can be re-esterified to promote lipid accumulation. GC administration to mice increase the availability of circulating lipid substrate by promoting lipolysis in the fasted state (61,62). The differences seen in the additive effects of GCs and insulin between omental and subcutaneous adipose tissue depots may point to a greater role for the omental depot driving hepatic steatosis (34).

Glucocorticoids, NAFLD and Muscle.

NALFD is associated with sarcopaenia and individuals with low muscle mass have a higher risk of developing NAFLD (63,64). Given the well-described detrimental effects GCs have on muscle, an indirect mechanism of NAFLD from myokine secretion, protein mediator or increased insulin resistance is plausible (20,65).

Glucocorticoid Receptor and NAFLD

There is a growing body of evidence for the role of the glucocorticoid receptor (GR) in the pathogenesis of NAFLD/NASH. The GR comprises a C-terminal ligand-binding domain, a central DNA binding domain, which interacts with specific DNA sequences of target genes and an N-terminal hyper-variable region. The classical activation pathway involves GC binding to the GR causing disassociation of the associated protein complex and subsequent translocation into the cell nucleus. Following translocation, gene transcription is altered by binding of the GR complex to specific DNA sequences known as glucocorticoid response elements (GRE) in the promoter region of target genes (66,67). This alteration in gene transcription up-regulates anti-inflammatory protein synthesis and reduces expression of pro-inflammatory cytokines. Multiple complex interactions of ligand-bound GR with transcription factors has been described (68).

In vitro data

In vitro experiments have manipulated adipose tissue GR expression. GCs are potent regulators of adipocyte differentiation *in vitro* and loss of GR signalling decreases adipocyte maturation (69). In human adipocytes, siRNA knock down of GR prevents GC-induced expression of genes including GC-induced leucine zipper (GILZ), and limits the adipogenic profile of mature adipocytes reducing adiponectin and leptin expression (70). These findings were not observed with knockdown of the mineralocorticoid receptor, which is expressed at much lower levels in adipose tissue. Recently, a tissue-specific knock-out of adipose tissue GR expression has been described with reduced adipose tissue depot weights on high fat diet feeding, however, the impact upon development of NAFLD was not assessed (71).

In vivo animal models

In animal models, the GC-GR interaction in mouse hepatocytes has been shown to have a wide range of effects upon metabolic phenotype (72–74). Global GR knockout is embryonically lethal due to respiratory failure and a reduction in hepatic glucose production (75). However in the post-natal setting in rodents, global antagonism using the GR antagonist, RU38486 improves metabolic function (76). Whilst GR haploinsufficiency does not alter the metabolic responses to high fat diet feeding (77), tissue-specific deletion of the GR in liver has been shown to have beneficial effects including decreasing fasting glucose and insulin levels and reducing the progression to overt diabetes (78). Furthermore, anti-sense oligonucleotides directed against the GR have shown liver-specific effects, decreasing fasting hyperglycaemia, reducing fasting insulin levels and decreasing GC-stimulated hepatic glucose output (79,80). In addition, liver-specific targeting of the GR using adenoviral vectors and shRNA delivery decreased hepatic lipid accumulation mediated through increased Hairy Enhancer of Split 1 (HES1) protein expression (81). Therapeutic hepatic GR antagonism has been explored through tagging RU38486 to a bile acid residue in rodents and dogs. This approach decreased hepatic glucose production but the impact upon lipid homeostasis was not determined (82,83).

A variety of other GR associated binding proteins and related receptors have

also been implicated in modifying the GR action and altering metabolic phenotype although their tissue specific role (liver *vs.* adipose tissue) is not fully understood. The binding protein, FKBP52 is believed to be important in potentiating the actions of GC. Mice with heterozygous deletion of FKBP52 were more prone to the development of hepatic steatosis following high fat diet feeding. The mechanisms by which this occurred are not clear and seem to contradict studies with GR knock-down, however, this was associated with a putative switch between carbohydrate and lipid metabolism (84). Mediator subunit 1 (MED1) is another receptor binding protein that is important for normal GC-GR functioning in liver. Liver-specific deletion of MED1 protects against dexamethasone-induced hepatic steatosis and is associated with increased HES1 expression (85). Liver X receptors (LXRs) are members of the nuclear hormone receptor superfamily and have crucial roles in cholesterol and lipid metabolism. There are two isoforms (LXR α and β) and LXRβ KO mice are protected from hepatic steatosis despite elevated circulating GC levels and this has raised the potential of LXRβ as a therapeutic target to treat and prevent GC-induced hepatic steatosis (86). There are several adipose tissue-derived factors that are regulated by GR binding to GREs within their promoters and that have been linked to the development of hepatic steatosis. Angiopoietin-like 4 (ANGPTL4) is secreted from both adipose tissue and liver and is induced by GC treatment (87) and ANGPTL4 KO mice are protected from dexamethasone-induced hepatic TAG accumulation (88). Lipin-1 deficiency is associated with lipodystrophy and hepatic steatosis in mice (89) and expression is increased by GC treatment (90). Lipin-1 deficiency limits adipocyte TAG synthesis and therefore spill over of lipid into the portal circulation is likely to be an important mechanism driving hepatic TAG accumulation in these animals.

Clinical studies

Data on the role of the GR in NAFLD in humans is limited, although Ahmed et al demonstrated increased hepatic GR expression in patients with NASH compared to control patients (25). A small number of interventional clinical studies have examined the impact of GR antagonism. Prolonged use is not recommended, however, after short-term administration beneficial effects

have been seen. These include decreased triglycerides (91), changes in HDL metabolism (92), limitation of antipsychotic-induced weight gain (93,94) and reduced fasting glucose and enhanced insulin sensitivity (95,96). A detailed analysis of GR antagonism to modulate lipid homeostasis has not been undertaken, however, In patients with type 2 Diabetes Mellitus, GR – antagonism combined with inhibition of cortisol synthesis had equally beneficial effects to lower glucose and improve insulin sensitivity in those patients with and without NAFLD (95).

Glucocorticoids and appetite control

The impact of GCs to regulate food intake and energy expenditure has been reviewed extensively elsewhere (97). NAFLD is strongly associated with excess calorie ingestion, obesity and GCs are potent regulators of appetite and food intake (28,98). GR is expressed in appetite centres in the brain and GR signalling is involved in regulating neuropeptides involved in appetite (99). In rats, GCs administered centrally, increased neuropeptide Y (NPY) driving obesity (100), however models of GC excess have not supported a role for NPY, although increased agouti-related peptide inhibiting the anorexigenic effects of the melanocortin system may be important . Uchoa et al showed the role GCs played in the rat CNS in modulating neuropeptides involved in appetite and energy homeostasis (101). Adipocyte GR signalling in mice is important in stress response and energy metabolism (71). Leptin, secreted by adipocytes is involved in appetite regulation in the hypothalamus and it has a protective role in hepatic steatosis (102). Studies in rodents have shown an inhibitory effect of GCs on leptin action pre-disposing to ‘leptin resistance’ and weight gain (100,103). Expression of 11β-HSD1 is also present in appetite centres providing an additional level of pre-receptor regulation of GC availability to module the appetite response (104).

Pre-Receptor modulation of Glucocorticoid availability in NAFLD

11β-hydroxysteroid-dehydrogenase type 1 (11β-HSD1)

11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) regenerates cortisol from inactive cortisone and thus amplifies local GC action. It is highly

expressed in human liver and adipose tissue and has been implicated in the pathogenesis of NAFLD. Whilst global deletion of 11β-HSD1 is associated with a beneficial metabolic phenotype including increased hepatic insulin sensitivity (105), transgenic liver-specific over-expression of 11β-HSD1 increases hepatic TAG content (106). However, liver specific 11β-HSD1 KO mice are not protected from the effects of high fat diet feeding and accumulate hepatic TAG to a similar level as seen in wild type animals (107). Intra-peritoneal anti-sense oligonucleotides have ben administered to suppress hepatic 11β-HSD1 expression and whilst these animals were protected from the development of NAFLD, there was a concomitant decrease in adipose 11β-HSD1 expression (108). Furthermore, in a murine model of NAFLD, 11β-HSD1 expression was increased in visceral adipose tissue but not in the liver and was associated with increased portal circulation corticosterone concentrations (109).Taken together, these data highlight the important cross-talk between liver and adipose tissue in the development of NAFLD and would add weight to the argument that GC action in adipose tissue is a significant contributor (and perhaps plays the major role) in hepatic lipid accumulation. There is an emerging role for 11β-HSD1 in the regulation of metabolic phenotype associated with Cushing's syndrome. Global 11β-HSD1 KO mice are protected from hepatic steatosis induced by circulating GC excess administered via drinking water (30). In addition, adipocyte expression of lipolytic enzymes including HSL and ATGL was reduced. Subsequently, these observations, specifically in adipose tissue, have been endorsed using in vivo siRNA manipulation of 11β-HSD1 expression (62). Interestingly, the protective effects of 11β-HSD1 deletion were mediated by its actions in adipose tissue and not liver, highlighting the crucial role of GC metabolism and action in adipose tissue as a key driver to the development of NAFLD.

In humans, the activity of 11β-HSD1 in the liver has been shown to be reduced in obesity (110) although this is still debated and not a consistent finding (111). In patients with NAFLD, 11β-HSD1 activity has been shown to be the same or reduced when compared to matched controls (25,112). However, activity may be dependent upon the stage of disease In those patients with hepatic steatosis, 11β-HSD1 activity was reduced, yet in those

with NASH, activity was increased (25). A small number of studies have examined hepatic gene expression profiles, but their interpretation is difficult in the absence of accurate staging of disease. Results have been variable, and in patients with NAFLD, 11β-HSD1 expression did not correlate with hepatic fat content as assessed on liver biopsy, but did correlate with BMI (113). This contrasts with observations in rodent models (106). However, in patients with NASH, 11β-HSD1 gene and protein expression were elevated compared to controls (25). In an additional study, using a multivariate analysis in patients undergoing bariatric surgery, 11β-HSD1 expression in VAT was associated with NAFLD (109).

11β-hydroxysteroid-dehydrogenase type 1 (11β-HSD1) inhibition.

Based on these data there has been much interest in pharmacological targeting of 11β-HSD1 in metabolic disease including NALFD. Subcutaneous injection of Carbenoxolone, a non-selective 11β-HSD inhibitor, administered to rodents improved parameters of the metabolic syndrome including hepatic steatosis (114). Several studies using rodent models have examined the effects of selective 11β-HSD1 inhibitors upon liver phenotype (115,116). The majority of compounds used are still in early development with rodent models predominantly being used to assess safety and efficacy. There appears to be broad agreement that this approach is associated with decreased lipid accumulation and may have additive effects when combined with a Peroxisome Proliferative-Activated Receptor gamma agonist (117–120). A novel study utilised a mouse model with an anti-sense oligonucleotide to knock down 11β-HSD1 with resulted in significant reduction in hepatic TAG synthesis and deposition and protection from a western style obesity diet (108).

Recently, a phase 1b clinical trial has been published which examined the therapeutic potential of a selective 11β-HSD1 inhibitor (Merck compound R05093151) in patients with NAFLD. (121). 12 weeks of treatment did significantly reduce liver fat as measured by magnetic resonance spectroscopy compared to placebo, but the effects were modest.

A-ring-reductases

5α-Reductase

The two isoforms of 5α-reductase (5αR1 and 5αR2) are important regulators of GC action, increasing clearance and limiting GC availability to bind and activate the GR. 5αR1 and 5αR2 are both expressed in human liver, whilst only 5αR1 is expressed in mouse liver and this is important when interpreting data from rodent models (see below). In adipose tissue, 5αR1 and not 5αR2 is expressed. 5αR1 KO mice (and not 5αR2 KO mice) fed an American lifestyle-induced obesity syndrome diet are more prone to hepatic TAG accumulation compared to WT animals (24). Interestingly, these animals were also entirely protected from the development of NAFLD associated hepatocellular carcinoma, although the mechanisms that underpin these observations have not been elucidated. Additional studies using differing dietary interventions as well as pharmacological inhibition have also demonstrated hepatic steatosis and increased fibrosis in 5αR1 KO mice (122). It remains to be determined whether these effects are mediated exclusively by actions upon GC availability, or whether modulation of androgen availability has an additional role to play.

Observational clinical studies have demonstrated a robust relationship between 5α-reductase activity as measured by urinary steroid metabolites and metabolic phenotype. Activity increases with BMI and decreases with weight loss and in addition predicts the future development of an adverse metabolic phenotype (123–125). Specifically in the context of NAFLD, 5αR activity is generally reported as increased (113) and isotope clearance studies using liquid chromatography tandem mass spectrometry have demonstrated increased cortisol clearance (126) .Differences in activity according to stage of disease have also been proposed with increased 5αR activity in patients with NASH and not simple steatosis.

Liver biopsy data have not demonstrated clear results. Decreased 5αR2 gene expression levels have been observed in patients with NASH (25), but in other studies, mRNA levels of hepatic 5αR1 and 5αR2 were not different across

the spectrum of NAFLD or from control patients (24). However, immunohistochemical staining suggested increased 5αR1 and not 5αR2 protein levels with increasing severity of NAFLD. A single clinical study has examined the impact of 5αR inhibition on metabolic phenotype in detail and whilst dual inhibition of 5αR1 and 2 was associated with decreased peripheral insulin sensitivity, a specific effect on the liver could not be identified although specific measures of hepatic lipid accumulation before and after intervention were not performed (23).

5β-Reductase

The role of 5β-reductase in the regulation of metabolic phenotype and NAFLD has not been explored in detail. In addition to its role in clearing GCs, it has a fundamental role in bile acid synthesis. Activity of 5β-reductase as measured by urinary steroid metabolite analysis, increases with increasing hepatic steatosis in healthy individuals (112).

Conclusions and Future directions

NAFLD and its clinical consequences represent one of the most important health challenges that we face today. This is an area of significant unmet need as current diagnostic, staging and treatment options are limited. There is a now a wealth of data from *in vitro* cell systems, rodent models and clinical studies that have elegantly demonstrated to potent effects of GCs to drive this condition (Figure 1). Within the liver, GCs activate TAG synthesis and hepatic steatosis with interactions at the GR crucially important. Pre-receptor metabolism of GC also contributes to NAFLD development. Tissue metabolism of GCs alters tissue exposure to GCs and can protect or potentiate injury. In adipose tissue, GC metabolism increases lipolysis and increase NEFAs that subsequently drive NAFLD. GCs can drive peripheral insulin resistance and protein release, which may drive hepatic injury further. Given our incomplete understanding of the pathogenesis of NAFLD however

and importantly its progression through the spectrum of disease, further study is clearly warranted. GCs have the potential to modify the pathological processes that occur at all stages of NAFLD and therefore the ability to manipulate GC action has attractive therapeutic potential. More detailed studies examining the prolonged effects of manipulation of pre-receptor GC availability are needed as well as further exploration of the mechanisms that regulate liver and adipose GR activation. Specifically targeting GR activation in a tissue specific manner may provide a novel approach to the treatment of NAFLD, but presents significant challenges.

Figure 1 - Multiple mechanisms in both liver and adipose tissue contribute to the development of NAFLD.

GCs bind to the GR and affect lipid in both adipose and hepatic tissue. Pre receptor regulation (via 11β-HSD & 5αR activity) can alter tissue GC exposure and GC-GR interaction is regulated by proteins such as Stat5, FKBP52, HES1, MED1, ANGPTL4 and LXRβ. In adipose tissue, GCs, in the fasting state, mobilise lipid by increasing Hormone sensitive Lipase (HSL) and Desnutrin (ATGL - which hydrolyses Triglyceride). In the fed state GCs are lipogenic by increasing expression and activity of DGAT. Expression of Lipases, Acyl Co Carboxylases and Fatty Acid Synthases (LPL, ACC and FASN) are also increased. GCs indirectly affect hepatic steatosis by altering the release of NEFAs and adipokines from adipose tissue. GCs directly affect liver and increase DNL by altering matrix Acyl Co-A Dehydrogenase. GCs increase TAG accumulation by increasing expression of DGAT and reducing TAG Hydrolase (TGH), involved in synthesis. NEFAs are re-esterified in the liver into lipid droplets.

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