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Review

Role of glucocorticoids and the glucocorticoid receptor in metabolism: Insights from genetic manipulations☆

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ABSTRACT

Since the discovery of the beneficial effects of adrenocortical extracts for treating adrenal insufficiency more than 80 years ago, glucocorticoids and their cognate, intracellular receptor, the glucocorticoid receptor have been characterized as critical checkpoints in the delicate hormonal control of energy homeostasis in mammals. Whereas physiological levels of glucocorticoids are required for proper metabolic control, aberrant glucocorticoid action has been linked to a variety of pandemic metabolic diseases, such as type II diabetes and obesity. Based on its importance for human health, studies of the molecular mechanisms of within the glucocorticoid signaling axis have become a major focus in biomedical research. In particular, the understanding of tissue-specific functions of the glucocorticoid receptor pathway has been proven to be of substantial value for the development of novel therapies in the treatment of chronic metabolic disorders. Therefore, this review focuses on the consequences of endogenous and experimental modulation of glucocorticoid receptor expression for metabolic homeostasis and dysregulation, particularly emphasizing tissue-specific contributions of the glucocorticoid pathway to the control of energy metabolism.

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1. Introduction

Cortisol, the natural glucocorticoid (GC) hormone in humans, as well as the numerous synthetic GCs used in therapy, exert a plethora of effects in the body. Secretion of GCs by the adrenal cortex is under control of a neuroendocrine feedback system, the hypothalamo-pituitary–adrenal (HPA) axis. Activation of the HPA axis starts with the secretion of hypothalamic corticotropin releasing hormone (CRH), the activation of pituitary pro-opiomelanocortin (POMC) gene transcription in response to

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CRH, secretion of the POMC-encoded adrenocorticotropic hormone (ACTH) and the ACTH-induced stimulation of GC synthesis in the adrenal glands. GCs, in turn, control the regulation of basal activity of the HPA axis, as well as the termination of the stress response by acting at extrahypothalamic centers, the hypothalamus and the pituitary gland, thereby limiting the systemic exposure time of the organism to GCs [1–6], and establishing a regulatory feedback loop.

At the molecular level, HPA activity, the subsequent modulation of systemic GC tone, and its translation into peripheral effects are mediated through cell-specific actions of the glucocorticoid receptor (GR), which represents a member of the hormone receptor subclass of the nuclear receptor superfamily of DNA-binding transcription factors. GR knockout animals are not viable, demonstrating the critical importance of functional GR action for survival [2]. Apart from its DNA-binding-dependent activity, large parts of tissue-specific GR action also rely on its direct protein–protein interaction capabilities with other transcriptional regulators and the subsequent control of distinct subsets of target genes. This is reflected by the survival of transgenic mice carrying a mutant GR compromised in its ability to bind DNA but not to other proteins [7], however it should be noted that GR DNA-binding domain mutants which lack the ability to dimerize can still bind to a subset of GR responsive promoters [8] and thus it remains unclear whether GR DNA-binding activity is dispensible for development and survival.

2. Molecular mechanism of GR action

2.1. Pre-receptor control of GR action

The activation of intracellular GR transcriptional activity is determined by its GC ligand-dependent activation (Fig. 1). As a consequence, the intracellular bioavailability of GCs represents a first critical checkpoint for GR activation, a process that has been termed “pre-receptor ligand control” and that is composed of the 11β-hydroxysteroid dehydrogenase (11β-HSD) enzyme system [9]: whereas the oxidative 11β-HSD type 2 isozyme catalyzes the conversion of cortisol to the inactive GC metabolite cortisone, 11β-HSD type 1 reduces cortisone to the bio-active cortisol [10], thus promoting local regeneration of cortisol, particularly in the GC-responsive metabolic tissues of the liver, fat, the lung and the central nervous system [11,12]. Based on a cell-type-specific expression pattern and selective activation of the 11β-HSD promoters [13], the relative levels of 11β-HSD enzymes are important factors in determining the intracellular concentration of cortisol [12,14], and have thereby emerged as potential regulators of metabolism and drug targets in GC-related disorders [15,16], prompting the design of 11β-HSD1 inhibitors for the treatment of the Metabolic Syndrome [11,17].

Indeed, 11β-HSD1-knockout mice are protected from high-fat diet-induced pre-adipocyte differentiation and obesity, and specific aspects of GC-mediated diabetes are improved in these mice

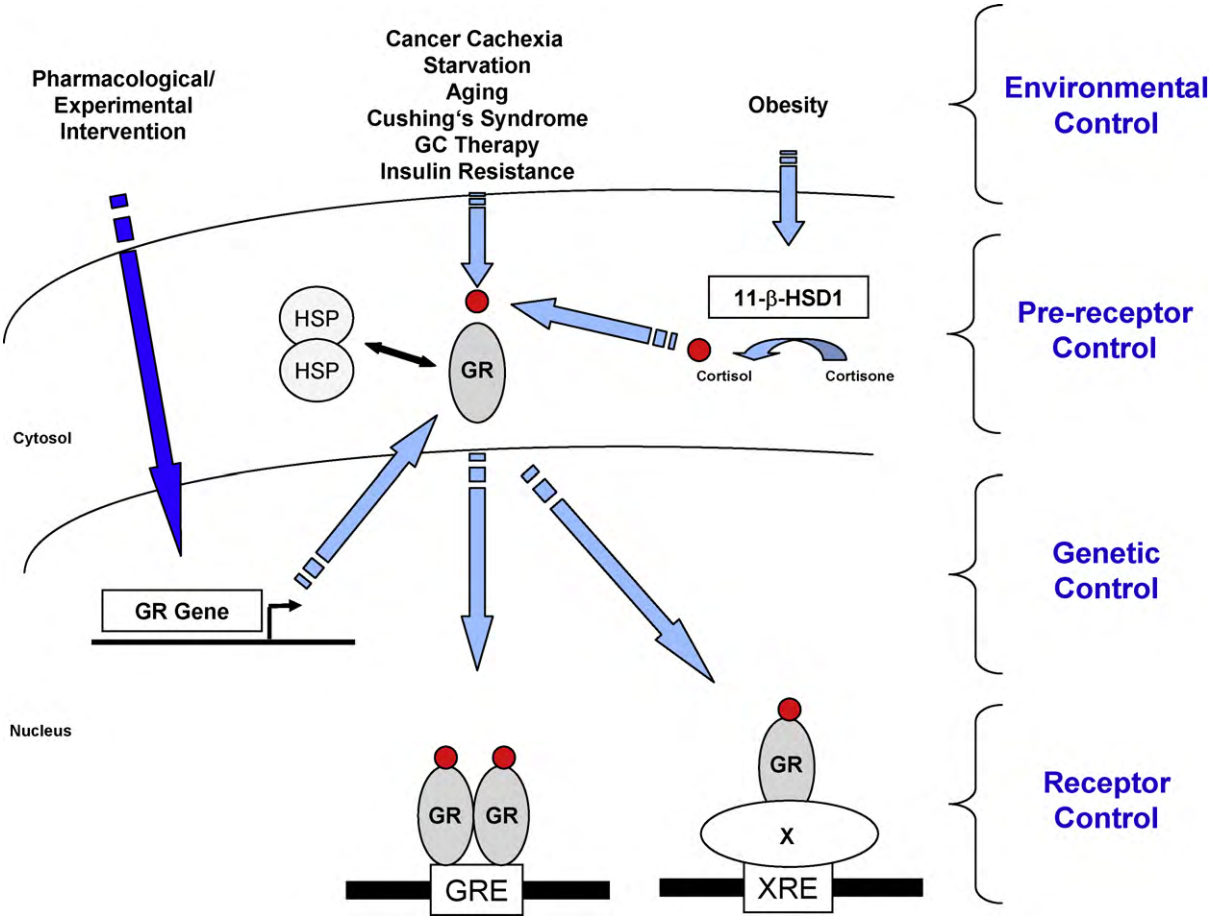

Fig. 1. Physiological, cellular and molecular regulation of the glucocorticoid receptor. As shown, there are multiple levels of control of GR activity and target gene expression. GR expression and activity can be manipulated by pharmacological means as well as genetic manipulation to alter the expression, ligand sensitivity and DNA-binding activity. Also, certain environmental factors can alter the systemic and intracellular GC availability. 11-β-HSD1, 11-β-hydroxysteroid dehydrogenase 1; GC, glucocorticoid; GR, glucocorticoid receptor; GRE, glucocorticoid response element; HSP, heat shock protein; X, variable factor; XRE, response element for variable factor. Major focus of current review highlighted in dark blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

[18–21]. By contrast, hepatic overexpression of 11β-HSD1, and the subsequent elevation of local GC levels is sufficient to trigger mild insulin resistance, hepatic steatosis and increased hepatic lipid synthesis/flux [22]. Associated with hepatic 11β-HSD1 overexpression and lipid accumulation, expression levels of nuclear receptors LXRα and PPARα have been found to be elevated in these animals [22]. Furthermore, mice that overexpress 11β-HSD2 specifically in adipocytes are protected from high-fat diet-induced obesity [23]. Consistently, elevated levels of adipose tissue 11β-HSD1 mRNA [24–26], and decreased levels of 11β-HSD2 mRNA have been found in clinical studies in obese patients [25], and human obesity has been associated with increased cortisol levels in adipose tissue as compared to lean counterparts [27]. In addition, there is higher expression of 11β-HSD1 in the liver and adipose tissue of obese individuals which may contribute to metabolic dysfunction in these individuals [28].

Together, these studies highlight the importance of GC pre-receptor ligand metabolism as a critical regulatory level for intracellular cortisol bioavailability and, consequently cell-type-specific GR transcriptional activity.

2.2. Receptor-dependent mechanisms of GC/GR action

At the cellular level, GCs act through the GR, a member of the nuclear receptor family [29]. In the absence of ligand, GR is retained in the cytosol as part of a chaperone-containing multi-protein complex, which maintains a high affinity for the ligand (Fig. 1). Evidence from various model organisms indicates that the heat shock proteins (Hsp) 70 and 90 are indispensable for GR folding, its hormone binding, nuclear transport, activation of transcription, nuclear retention and degradation. The modulation of GR activity by the Hsp70 and Hsp90 chaperone machinery is a complex process, modulated by changes in the concentrations of their respective co-chaperones, which probably respond to changes in the cellular environment. The co-chaperones can roughly be separated into an "activating" subclass, such as Hsp40, Hip, Hop, and most immunophilins, and those that play an inhibitory role for GR transcriptional activity, such as Bag-1 or CHIP [30]. In addition, a recent study has shown that GR transactivation is modulated by a physical interaction with an adapter protein within the nucleus, namely modulator of non-genomic action of the esterogen receptor (MNAR), the nature of which is complex and depends on cell type [31]. Lastly, it is now clear that tissue GC sensitivity depends not only on GR expression but is modulated by many factors and this is exemplified by a study which identified several novel genes, including type II bone morphogenic receptor (BMPRII), which may influence GC sensitivity [32], the mechanisms of which remain largely unknown.

Upon hormone binding, GR translocates to the nucleus, where it acts as a transcriptional regulator of distinct GC-responsive target genes via direct DNA binding or through protein–protein interactions with other transcriptional regulators [29] (Fig. 1). The GR subunits homodimerize and bind DNA at glucocorticoid response elements (GREs) in the promoter region of target genes [33]. Interestingly, the GR has been found to rapidly cycle on and off DNA-binding elements (or other DNA-bound transcription factors), both in the presence and absence of hormone [34,35]. Molecular chaperones might also facilitate this process as GR–Hsp co-localization and direct physical interaction in the nucleus and on chromatin templates has been experimentally demonstrated both in the unliganded and ligand-bound state [36–39]. This on–off kinetics would allow other components of the transcription machinery to bind the GR complex, and facilitate GR activity adjustments in response to changing cellular environments and varying ligand concentrations [30] (Fig. 1).

Interestingly, recent studies demonstrated that the GR seems to predominantly bind to nuclease-accessible sites, and that accessibility, in turn, is either constitutive or ligand-induced [40]. In this scenario, both constitutive and inducible GR recognition sites can be subdivided into distinct sub-categories as determined by their requirement for different chromatin modifying complexes, particularly the Brg1-Swi/Snf-containing complex [40]. As the pattern of GR accessible sites was found to be highly cell-type-specific [40], these findings implicate an as yet not well-understood mechanism of GC/GR activity control at the chromatin level. Indeed, structural studies have shown that even one base pair differences in distinct GR DNA recognition sites differentially affect GR confirmation and transcriptional activity [41], suggesting that DNA itself can serve as an allosteric ligand for the GR, thereby determining gene-specific GR action and subsequently downstream GC-dependent cellular pathway activity.

In this setting, it can be envisaged that both GC ligand binding and DNA sequence specificity cooperatively determine gene-specific GR confirmation and co-activator recruitment, which in turn is critically dependent on GR confirmation and modular structure [29]. The GR contains a central domain harboring two zinc fingers as a dimerization and DNA-binding interface. The C-terminal ligand-binding domain (LBD) is responsible for high affinity binding of GCs, thereby overlapping with the activation domain/function AF2, which is particularly exposed after a conformational change induced by ligand binding and/or DNA contact [42]. Whereas the exposed AF2 then serves as an interaction platform for associated co-activator complexes, the N-terminal part of the GR contains AF1, a ligand-independent activation function, required for basal transcriptional activity and association with basal transcription factors [42].

Noteworthy, important GC functions seem to be mediated via the so-called non-genomic mechanisms. These processes include the intercalation of GCs in cellular membranes and the subsequent alterations of cation transport or mitochondrial proton leak [43]. In addition, cytosolic GR has been found to induce the rapid release of Src kinase from cytoplasmic GR–Src complexes, resulting in the inhibition of arachidonic acid release in specific cellular contexts [44]. Finally, a number of rapid GC effects have been proposed to occur via membrane-bound GR as demonstrated for the integration of the GR into the T-cell receptor multi-protein complex [45] and at least some aspects of GR signaling may occur though its interaction with caveolin-1 enriched caveolae [46]. Despite their potential importance for therapeutic approaches in inflammatory and autoimmune disease, mechanisms of non-genomic GC/GR action remain largely undefined [47].

3. Conditions of pathophysiological GC/GR activity

Under normal conditions, the pancreatic β-cell hormone insulin triggers the fast uptake and non-oxidative metabolism of glucose in liver, muscle, and adipose tissue, and simultaneously inhibits glycogenolysis and gluconeogenesis in liver during feeding [48–50]. As a counter-regulatory opponent of insulin's anabolic functions, tight control of GC release and tissue-specific activity is required for proper metabolic regulation in response to changing environmental conditions, e.g. fasting and/or starvation [16,51–54], and dysfunctional GR signaling is associated with a number of severe metabolic pathologies, including cancer cachexia and sepsis [55,56].

The importance of the GC/GR endocrine axis for energy homeostasis is most dramatically exemplified by states of either endogenous or exogenous GC deficiency or excess, e.g. Addison's disease and Cushing's syndrome, respectively. Addison's disease is caused by autoimmunity against the adrenal cortex, inherited GC

synthesis dysfunction or pituitary disease. The resulting deficiency in proper GC action is associated with impaired stress resistance, lymphoid tissue hypertrophy, weight loss and hypoglycemia [57].

In contrast, Cushing's patients with sustained and pronounced hypersecretion of GCs due to pituitary adenomas or ectopic, ACTH-producing tumors and a subsequent elevation of circulating GC levels display central obesity, increased breakdown of skeletal muscle mass, hyperglycemia, hepatic steatosis, hypertension, elevated cholesterol, immunodeficiency, and insulin resistance [58]. Similar phenotypes represent typical side effects of long-term anti-inflammatory and immunosuppressive GC therapy [59–61].

Remarkably, many of the aforementioned complications of GC excess represent also prototypical components of the so-called Metabolic Syndrome [62]. Indeed, hyperactivity of the HPA axis is positively correlated with the Metabolic Syndrome as demonstrated in subjects with glucose intolerance, hypertension, and insulin resistance [63–66]. Together, the Metabolic Syndrome disease cluster, including obesity, hyperglycemia, dyslipidemia, hypertension, and insulin resistance, can precipitate into severe end-stage diseases such as type II diabetes, atherosclerosis and cardio-vascular complications [62], and is commonly associated with aging, a sedentary lifestyle, and a genetic predisposition [67].

Notably, diabetes mellitus frequently occurs during GC therapy and Cushing's syndrome [61], which can be partly attributed to the ability of the GC/GR axis to suppress insulin output from the pancreatic β-cell [68]. Also, mice overexpressing the GR in pancreatic β-cells feature decreased insulin secretion accompanied by reduced glucose tolerance in adult mice and hyperglycemia in aged mice [69,70].

Apart from defective pancreatic insulin output, systemic insulin resistance represents a hallmark of the Metabolic Syndrome that can be directly linked to GR action: GCs have been found to directly influence insulin sensitivity by interfering with components of the insulin-signaling cascade. GC treatment leads to a downregulation of insulin receptor substrate (IRS) 1 and 2 proteins, blunting intracellular insulin signal transduction [71]. Additionally, phosphoinositide 3 (PI3) kinase activity as well as Akt phosphorylation as markers of insulin-signaling strength represent negative targets of the GC/GR axis [72,73].

In contrast to insulin resistance, obesity *per se* (e.g. obesity without diabetes) is not associated with increased systemic GC levels [12], but rather features enhanced GC pre-receptor generation through induction of 11β-HSD1 activity, which has been shown to essentially contribute to the obese phenotype as discussed above [14]. Notably, excessive GC/GR tone as observed in Cushing's syndrome has been identified to be instrumental for the obesity in these patients [16], and consistent with the particularly disruptive impact of central (abdominal) obesity on insulin sensitivity [74,75], also Cushing's patients are characterized by a redistribution of body fat from the periphery to central/abdominal depots [58,76–79].

The broad spectrum of metabolic complications associated with aberrant GC levels mostly reflects impairments of tissue-specific GC activity in metabolically active organs. In addition to alterations of systemic and/or local GC levels and tone, also endogenous and experimental changes in the levels of GR gene expression substantially impact normal and dysfunctional energy homeostasis, and will be discussed below.

4. GR expression, regulation and function in metabolically active tissues

Typically, blood GC concentrations rise during conditions of stress such as prolonged fasting, during physical exercise and during trauma and contribute to alterations in metabolism such as increased lipolysis in skeletal muscle and adipose tissue, decreased glucose uptake in muscle and fat as well as increased gluconeogenesis in the liver to maintain blood glucose levels, and perhaps blunted protein synthesis in muscle [42]. This section will particularly highlight new information on genetic manipulations of the GR that alter tissue GC sensitivity.

A general role of the GR in metabolism was made clear from studies of people with chronically high GC levels from which develops truncal obesity, hypertension, skeletal muscle wasting and impaired glucose homeostasis due to lower insulin sensitivity [80]. Furthermore, treatment with synthetic GCs such as Dexamethasone (Dex) results in systemic insulin resistance and hepatic dyslipidemia [81]. But what about the GR? There are certain GR variants, albeit rare, expressed by individuals which can also lead to a higher risk of obesity [82]. In particular, studies have consistently shown that individuals with a *BclI* polymorphism in intron 2 of the GR gene exhibit higher incidence of obesity and insulin resistance [83,84] although this is controversial [85]. In addition, another GR polymorphism, which results in lower GC sensitivity presumably by increasing the expression of a ligand-insensitive GR variant [86] is associated with low insulin and cholesterol levels [87]. In any case, these polymorphisms appear to have rather mild effects with respect to GR function and expression as well a metabolic phenotype. In contrast, transgenic expression of a GC-hypersensitive GR mutant in mice was able to alter the basal regulation of the HPA, thereby increasing susceptibility to the development of hypertension upon low-dose Dex exposure [88]. In line with this, whole-body GR haploinsufficiency results in hypertension in mice, probably due to altered rennin–angiotensin–aldosteron system [89]. Furthermore, cardiomyocyte-specific GR overexpression resulted in major ion channel remodelling manifesting in altered electrical activity of the heart without abnormal cardiac hypertrophy or fibrosis [90] suggesting that cardiac problems may arise as a result of heightened systemic GC tone.

Also, studies of rodents show that excess GC exposure in the perinatal period can program liver and skeletal muscle metabolism in favour of a poor metabolic phenotype in later life [91] probably because of upregulated GR expression and GC sensitivity in visceral fat and liver [92,93]. Altogether, it is clear that apart from altered GC homeostasis also GR expression/activity can influence whole-body metabolism.

4.1. GR and skeletal muscle metabolism

Skeletal muscle, by virtue of its relative mass, is a quantitatively important tissue for metabolism. Indeed, impaired insulin action in skeletal muscle is believed to account for the majority of the defect in insulin-stimulated glucose disposal in obese, insulin-resistant as well as diabetic individuals [62]. As previously summarised, increased GR activity in skeletal muscle leads to lower net protein synthesis and insulin-stimulated glucose uptake [42]. In particular, although correlative, a study has shown associations between the level of GR mRNA in myotubes cultured from skeletal muscle biopsy samples and % body fat, systolic blood pressure and *in vivo* insulin resistance [94]. Also, GR mRNA expression in skeletal muscle of diabetic patients correlates with the degree of insulin resistance, with a normalisation of GR expression following treatment to improve insulin sensitivity [95]. Taken together, these studies suggest that higher muscle GC sensitivity as reflected by elevated intramuscular GR expression levels contribute to the Metabolic Syndrome phenotype.

Treatment of muscles *in vivo* or *ex vivo* with Dex blunts insulin-stimulated glucose uptake, insulin signaling, GLUT4 translocation and glycogen synthase activation [96–98]. While no study has examined whole-body or muscle-specific genetic manipulation of GR, insights on the role of GR in muscle metabolism can still be

gained from studies which employed adrenalectomy or GR antagonists to block GR activity. In particular, GC levels are relatively high in obese db/db mice and adrenalectomy of these mice resulted in improved insulin-stimulated muscle glucose disposal [99]. In line with this, insulin resistance in hind limb muscles induced by high-fat diet was ameliorated by treatment with the GR antagonist RU486 [100]. Furthermore, a recent study showed that the acute and potent muscle insulin resistance, as indexed by muscle insulin signaling, induced by haemorrhage trauma was completely reversed by treatment with agents that block GC synthesis and GR action [101].

GCs also affect muscle protein metabolism probably by promoting protein breakdown and inhibiting muscle protein synthesis [42]. Experiments using adrenalectomised rats or treatment with GR antagonists demonstrated an involvement of GCs in the induction of ubiquitin-mediated protein degradation during starvation and during sepsis [102]. On this, a recent study has demonstrated that muscle-specific GR deletion prevents the increase in skeletal muscle proteolysis induced by diabetes via a non-genomic action of GR to bind to and blunt the activation of the insulin-signaling intermediate PI3K by interfering with IRS1–PI3K complex activation during hyperinsulinemia [103]. On the other hand, Waddell et al. recently showed that Dex-mediated upregulation of Murf1, an important and muscle-specific ubiquitin E3 ligase, was blunted in mice expressing a dimerization-deficient form of the GR, suggesting that GR-induced upregulation of Murf1 may be involved in muscle wasting during excess GC exposure [104]. Skeletal muscle protein synthesis also decreases during fasting, and GC blunt this via interfering with insulin and nutrient stimulated mTOR–p70s6k pathway [105], the mechanism of which is likely to involve the upregulation of the expression of the mTORC1 inhibitor protein, REDD1 [106]. Clearly, further studies using genetic manipulations of GR expression/activity are required to fully define and clarify the role of the GR in muscle metabolism.

4.2. GR and adipose tissue metabolism

The particular occurrence of central or truncal obesity has been linked to insulin resistance [107]. Consistent with an involvement in the GC–GR axis in this phenotype, patients with Cushing's syndrome are characterized by a redistribution of body fat from the periphery to the central depots [107]. These fat depots consist of adipocytes which are relatively GR-rich and are thus more sensitive to the actions of GCs [77]. Furthermore, GR mRNA expression is upregulated in abdominal fat depots of insulin-resistant, hypertensive rats exposed to a high-salt diet [108]. Also, GCs impact upon different fat depots differently, where they increase lipolysis by inducing hormone-sensitive lipase [109] and reduce lipoprotein lipase (LPL) activity in peripheral fat depots; they promote pre-adipocyte differentiation, pro-lipogenic pathway activity, and thereby cellular hypertrophy in central fat [110,111]. GCs have also been shown to impact upon adipose tissue insulin action in that they decrease insulin sensitivity by blunting glucose uptake, proximal insulin signaling and subsequent GLUT4 translocation as well as glycogen synthase activation [73,98,112]. Consistent with this, GCs downregulate glucose uptake capacity and insulin-signaling proteins in omental but not subcutaneous human adipocytes [113].

4.3. GR and liver metabolism

The liver plays a pivotal role in regulating whole-body carbohydrate, fat and protein metabolism. The role of the GR in regulating local liver metabolism is summarised in Fig. 3. In particular, during conditions of energy deprivation such as during fasting or exercise, systemic GC concentrations rise and this is sensed by the GR in the liver which then coordinates changes in metabolism to mobilise glucose for other tissues such as the brain and skeletal muscle. Indeed, mice which lack GR in hepatocytes exhibit profound hypoglycemia after prolonged fasting most likely due to the abnormal lack of upregulation in the expression of key gluconeogenic enzymes such as phosphoenol pyruvate carboxykinase (PEPCK) [114]. This mechanism is via direct DNA binding to promoter regions of the gluconeogenic genes as evidenced by a lack of Dex-induced upregulation of PEPCK in livers of mice expressing a DNA-binding defective GR mutant [7]. A defining characteristic of diabetes is abnormally high blood glucose in the fasted state and a lack of suppression of endogenous glucose production during feeding which are both mediated by abnormally high rates of net hepatic glucose production [42], which is likely to be explained by higher GC action on PEPCK gene expression [115]. In rodent models of diabetes such as ZDF rats and ob/ob mice, the total expression of GR in the liver was found to be low despite a much larger activation of GR-dependent transcription when compared with healthy controls [116,117]. In contrast, others have observed higher liver GR expression in diabetic db/db mice [118]. While the differences in liver GR expression between these studies are not easily explained, the mRNA expression of GR target genes such as PEPCK and GR abundance in the nucleus are typically starkly higher in the livers of both of these rodents models in the fed state [116,118], indicative of a much higher GC action and GR turnover in the liver of diabetic animals. On the other hand, changes in liver GR expression are not evident in other models of insulin resistance, as long-term (i.e. >30 wk) treatment with high-fat diet does not alter liver GR expression and expression of GR target genes [119], indicating that liver GC sensitivity is not always altered under conditions of low whole-body insulin action.

So, liver GR expression and activity are altered in some models of poor metabolic phenotype but do these changes play a causal role in dysfunctional metabolism in these conditions? On this, while studies have shown that a diabetic-like metabolic phenotype can be partially reversed by GR antagonists and reducing systemic GC levels by adrenalectomy [119–122], the conclusions from these studies are clouded by the potential off-target effects of these treatments. While whole-body GR deficiency in mice does not alter body-weight gain, impaired glucose tolerance and liver triglyceride accumulation associated with administration of a high-fat diet [89], a recent study has shown that the downregulation of GR mRNA and activity via administration of an 11β-HSD inhibitor reduced the weight gain, hyperglycemia and insulin resistance in response to high-fat diet feeding in mice [119]. In accordance with this, inhibition of GR expression by agonists for nuclear receptor liver X receptor (LXR) results in an amelioration of the diabetic phenotype in obese, db/db mice [121]. A more recent study has shown that downregulation of liver, but not adrenal gland, hypothalamus or pituitary GR expression by antisense oligonucleotide treatment improved fasting hyperglycemia and systemic glucose homeostasis in diabetic mice without affecting blood GC levels [123]. A similar study showed that treatment of diabetic rodents (i.e. ob/ob, db/db mice and ZDF rats) *in vivo* with GR antisense oligonucleotides to downregulate GR expression resulted in an improved fasting hyperglycemia and insulinemia, which was partially explained by a complete blunting of Dex stimulated hepatic glucose production as assessed by *ex vivo* experiments [124]. However, the expression of GR in other tissues such as adipose tissue and muscle was also likely to be affected by this treatment, and may have affected liver function indirectly. The progression to frank diabetes by streptozotocin treatment, as indexed by fasting hyperglycemia and hyperinsulinemia, was blunted in mice with hepatocyte-specific GR knockout [114]. Taken together, there is a strong line of evidence that hepatic GC and GR action impact on gluconeogenesis and that dysregulation of hepatic GR activity contributes to the pathogenesis of insulin

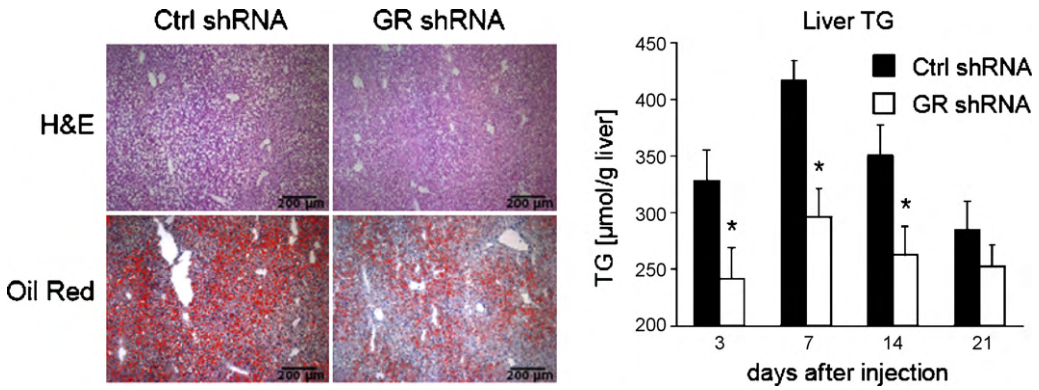

Fig. 2. Liver specific GR knockdown alleviates hepatic steatosis in obese, diabetic mice. Shown in the left panel are liver sections from a representative control (Ctrl) or GR shRNA adenovirus-injected db/db mouse 7 days after injection stained with haematoxylin/eosin (H&E) or Oil Red O, which stains neutral lipids. The unstained vacuoles visible in the H&E sections of the GR knockdown mice stain positive (red color) for lipids with Oil Red O. Shown in the left panel are biochemically determined liver triglyceride (TG) levels of control (Ctrl) or GR shRNA adenovirus-injected db/db mice various time points after injection as indicated (means ± SEM, $n = 5$). Adapted from Lemke et al. [81] with permission. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

resistance, at least at the late stage, when overt hyperglycemia and frank diabetes manifests. On the other hand, hepatic GR activity also impacts upon the action of insulin to suppress hepatic gluconeogenesis [125], which is an earlier defect in obese and insulin-resistant individuals [62], however, to our knowledge, thus far no studies of GR gene manipulation have adequately addressed the role of GR in this process *in vivo*.

Dex and other GCs have been used clinically for decades to treat inflammatory disorders, and long-term treatment is commonly associated with hepatic steatosis [42]. It has been known for some

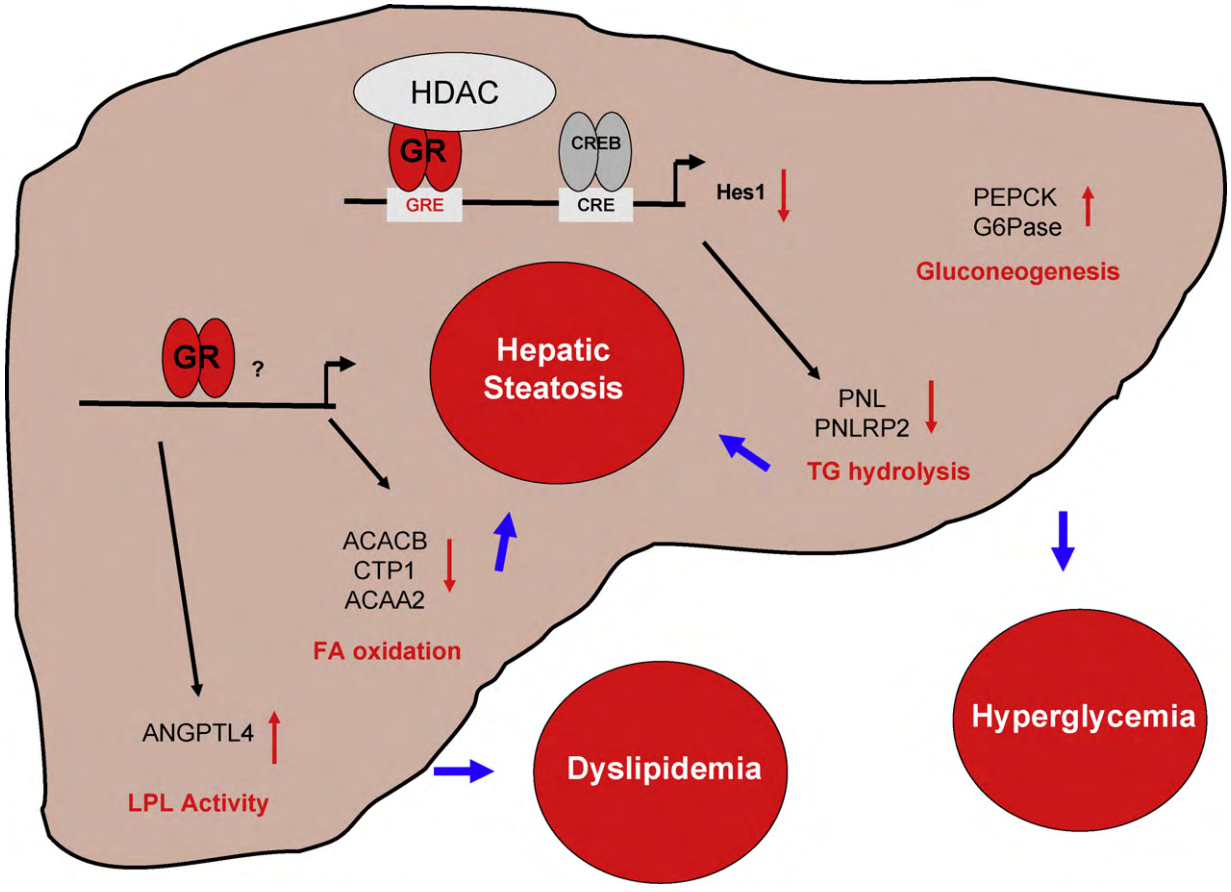

Fig. 3. Mechanisms by which excess GR activity leads to metabolic dysregulation in the liver. Excess glucocorticoid receptor (GR) activity can lead to fasting hyperglycemia and possibly blunted insulin-induced suppression of hepatic glucose production by heightened gene activation and expression of gluconeogenic genes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). On the other hand, chronic GR activation leads to excess triglyceride (TG) storage in the liver due to reduced catabolism of fatty acids (FA) via β-oxidation and reduced capacity to hydrolyse TG, the former via a reduction in Hairy Enhancer of Split 1 (Hes1) expression. Excess liver GR activity may also cause systemic dyslipidemia via increasing the expression and secretion of angiopoietin-like (ANGPTL) 4 leading to excess inhibition of lipoprotein lipase (LPL) activity in adipose tissue (see text for details). ACACB, acetyl-Coenzyme A carboxylase 2; ACAA2, acetyl-Coenzyme A acyltransferase 2; CPT1, carnitine palmitoyl transferase 1; CRE, cyclic AMP-responsive element; CREB, cAMP-responsive element binding protein; HDAC, histone de-acetylase; PNL, pancreatic lipase; PNLRP2, PNL-related protein 2.

time now that *in vivo* [126] and *in vitro* [127–129] treatment with GR agonists increase serum VLDL-triglyceride (TG) levels and hepatic lipid accumulation (Fig. 2). Compared with the abundance of literature concerning the role of the GR in hepatic gluconeogenesis (see above and [42]), information on the role and mechanism of the GR in lipid metabolism is less well defined. However, several recent studies have shed some new light on this aspect. In particular, a recent study by Watts et al. has shown that treatment of obese, diabetic rats with antisense oligonucleotides to downregulate liver and adipose tissue GR resulted in a lowering of blood levels of TG and non-esterified fatty acids in the fed state [124], however it was unclear how this phenotype arose and to which extent each tissue contributed. On this, a study from our laboratory has shown that liver specific disruption of GR action by adenoviral delivery of GR shRNA improves the steatotic phenotype and lowers serum VLDL-TG of fatty liver mouse models [81] (Fig. 2). This is in line with an earlier observation that plasma TG were substantially lower in mice with hepatocyte-specific GR knockout [114] and further studies of these mice showed that the GR promotes transient hepatocellular fat accumulation following partial hepatectomy [130]. The increase in TG accumulation with GR activation probably results from a downregulation of genes involved in hepatic TG lipolysis and β-oxidation of fatty acids, as well as an upregulation of fatty acid uptake and storage as liver GR knockdown alters these in an opposite manner [81]. So how might the GR orchestrate this series of changes in FA metabolism? Recent studies have shown that GR can modulate lipid metabolism by altering the expression of target genes involved in direct regulation of the expression and activity of FA and TG metabolic pathways. In particular, specific disruption of liver and hepatocyte GR results in upregulation of the transcriptional repressor hairy enhancer of split 1 (Hes1) which leads to an upregulation of pancreatic lipase expression [81]. In contrast, along with a fatty liver phenotype, Hes1 expression is downregulated with Dex treatment and in mouse models of the Metabolic Syndrome, and overexpression of Hes1 lowers liver TG in these conditions [81]. Another recently identified GR target gene is Angptl4 [131] which is upregulated during fasting and inhibits adipose tissue lipoprotein lipase leading to lower serum TG hydrolysis [132]. Since the Dex-induced hypertriglyceridemia and increase in liver TG can be blocked by knockout of Angptl4, the higher liver TG levels in cases of GR hyperactivity could be explained by alterations in the Angptl4-dependent flux of TG from adipose tissue to the liver [131]. In addition, the effects of GR action are modulated by the transcriptional co-activator MED1, as liver specific MED1 knockdown attenuates Dex-induced hepatic steatosis, probably via blunting the downregulation of FA β-oxidation [133]. Altogether, while some mechanisms by which the GR can modulate liver lipid handling have been revealed (Fig. 3), further work is clearly required to fully understand how the GR can orchestrate changes in several aspects of lipid metabolism.

There are also indications that GR activation can impact upon liver cholesterol handling and metabolism. In particular, we have recently shown that liver GR knockdown results in higher liver expression of sterol regulatory element binding protein (SREBP)2 and increases liver cholesterol levels but decreases serum cholesterol in obese mice [81]. This is in line with another study which demonstrated lower blood cholesterol with systemic GR knockdown in obese and diabetic rodents [124]. It will be interesting to determine which tissue and which mechanism might be responsible for the improved hypercholesterolemia upon reduced GR expression.

Lastly, there is little to no information as to whether GR action impacts upon hepatic protein metabolism. Thus, a clear avenue for future studies would be to pursue the role of GC–GR axis in physiological (e.g. fasting) and pathophysiological (e.g. diabetes) protein turnover in the liver.

5. New players in the GR–GC axis to modulate metabolism

Accumulating evidence has implicated oxidative stress, mainly in the form of reactive oxygen species (ROS), in the pathogenesis of complications associated with the Metabolic Syndrome, particularly insulin resistance. Increased systemic oxidative stress could be correlated with obesity in both humans and mice [134,135]. Notably, antioxidant treatment of diabetic/obese subjects has been partly successful in improving insulin sensitivity, glucose and lipid homeostasis [134–136]. Houstis et al. provided direct evidence for an involvement of ROS in GC-induced insulin resistance in adipocytes [136]. Dex treatment of 3T3-L1 cells resulted in elevated levels of ROS generation with a concomitant reduction of insulin sensitivity, which could be partly reversed by various antioxidant treatments [136]. In conclusion, oxidative stress appears to play a causal role in the emergence of insulin resistance and GCs might mediate at least some of their metabolic effects by increasing cellular ROS production.

Another hypothesis behind the progression of excess nutrient supply and insulin resistance is the link between increases in intracellular fatty acid species (i.e. diacylglycerol, ceramide) and blunted insulin signaling and action [137]. On this, a recent report showed that inhibition of ceramide synthesis by pharmacological means or in mice deficient in a ceramide synthesis enzyme partially blunted the Dex-induced decreases in systemic as well as muscle and hepatic glucose insulin sensitivity. Indeed, Dex promoted ceramide accumulation in the portal circulation and the liver, and induced hepatic expression of various key enzymes in ceramide and sphingolipid synthesis [138], providing a link between aberrant fat metabolism and altered glucose homeostasis in GC/GR action. Thus, it will be interesting to further explore the specific molecular functions of the GR within the ceramide metabolic pathway and its potentially integrating function for systemic energy homeostasis.

Lastly, it was recently shown that there is higher GR expression in brain limbic system of diabetic rats [139] which may contribute to the heightened drive of hypothalamic–pituitary axis in these animals.

6. Outlook

Here we have provided an overview of the role of the GR in modulating metabolism in major metabolic tissues; the liver, skeletal muscle and adipose tissue. While significant knowledge of the role of the GR in metabolism in these tissues exists (Fig. 3), we believe that there is still much more to learn. In particular, most of the knowledge regarding the role of the GR in muscle and adipose tissue come from the use of GR agonists or antagonists which may be difficult to interpret due to off-target effects. Thus, the use of new strategies such as tissue-specific knockout or overexpression will help to understand the role of the GR in these tissues greatly. Furthermore, it is important for future studies to measure multiple indices of GC sensitivity in tissues such as GR and 11β-HSD protein expression, DNA-binding activity, chromatin immunoprecipitation scanning [140] as well as GR target gene activation. On this, we have recently established a method which enabled us to visualize liver PEPCK gene activation *in vivo* [141], and we believe that the combination of these techniques adequately allows one to gain insight into the complexity of tissue-specific GC–GR action.

Corticosteroids are widely used for the treatment of inflammatory diseases. Obviously, the benefits of anti-inflammatory actions of the GR outweigh the disadvantage of metabolic and other side effects [61]. Nevertheless, side effects of steroid therapy remain a great hurdle, and research has focused on the development of the so-called 'dissociated steroids' [61]. These are selective GR agonists (SEGRAs) inducing GR-mediated trans-repression with little

or no effect on trans-activation. Since anti-inflammatory actions of GCs are predominantly based on trans-repression while many of the side effects on activation, these compounds could prove to be of great value for the treatment of acute or chronic inflammation [142,143]. The concept of SEGRAs has been validated through a genetic approach, namely by the analysis of mice expressing dimerization-deficient GR (GRdim). Thus, although certain activating functions of the GR were abolished, its anti-inflammatory effects were mostly preserved during endotoxemia [7].

As discussed above, application of a GR antagonist has been shown to improve metabolic abnormalities under certain conditions. However, complete suppression of GR-mediated anti-inflammatory pathways would probably result in deleterious side effects. Furthermore, it is becoming established that obesity and the Metabolic Syndrome in general are associated with subacute, chronic inflammation, which is likely to contribute to the development of insulin resistance and the progression to advanced disease [144]. In particular, a recent study has shown that there is an early reprograming of liver inflammatory gene expression which precedes hepatic steatosis in response to high-fat feeding [145] which suggests that this low grade inflammation may be an early response leading to an eventual pathogenic metabolic phenotype. In this respect, discovery of GR ligands that suppress GC-dependent metabolic abnormalities while maintaining anti-inflammatory properties will be of great future interest.

Dissection of the regulatory network around the GR can contribute to the development of targeted and specific strategies for pharmacological modulation of GC action. On this note, it will be crucial to characterize physical and functional interaction partners of the GR and the impact of their interaction on regulation of downstream pathways controlling metabolism.

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