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► **To cite this version:**

Alexandros Vegiopoulos, Stephan Herzig. Glucocorticoids, Metabolism and Metabolic Diseases. *Molecular and Cellular Endocrinology*, 2007, 275 (1-2), pp.43. 10.1016/j.mce.2007.05.015 . hal-00531932

**HAL Id: hal-00531932**

**<https://hal.science/hal-00531932v1>**

Submitted on 4 Nov 2010

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## Accepted Manuscript

Title: Glucocorticoids, Metabolism and Metabolic Diseases

Authors: Alexandros Vegiopoulos, Stephan Herzig

PII: S0303-7207(07)00210-9  
DOI: doi:10.1016/j.mce.2007.05.015  
Reference: MCE 6662



To appear in: *Molecular and Cellular Endocrinology*

Received date: 22-2-2007  
Revised date: 14-5-2007  
Accepted date: 17-5-2007

Please cite this article as: Vegiopoulos, A., Herzig, S., Glucocorticoids, Metabolism and Metabolic Diseases, *Molecular and Cellular Endocrinology* (2007), doi:10.1016/j.mce.2007.05.015

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## **Glucocorticoids, Metabolism and Metabolic Diseases**

**Alexandros Vegiopoulos and Stephan Herzig§**

**Molecular Metabolic Control, German Cancer Research Center Heidelberg, Germany**

**§ Corresponding author:**

**Stephan Herzig, PhD**

**German Cancer Research Center Heidelberg**

**Molecular Metabolic Control A170**

**Im Neuenheimer Feld 280**

**69120 Heidelberg**

**Germany**

**Phone: +49-6221-42 3593**

**Fax: +49-6221-42 3595**

**Email: [s.herzig@dkfz.de](mailto:s.herzig@dkfz.de)**

### ***Abstract***

Since the discovery of the beneficial effects of adrenocortical extracts for treating adrenal insufficiency more than 80 years ago, glucocorticoids (GC) and their cognate, intracellular receptor, the glucocorticoid receptor (GR) have been characterized as critical components of the delicate hormonal control system that determines energy homeostasis in mammals. Whereas physiological levels of GCs are required for proper metabolic control, excessive GC action has been tied to a variety of pandemic metabolic diseases, such as type II diabetes and obesity. Highlighted by its importance for human health, the investigation of molecular mechanisms of GC/GR action has become a major focus in biomedical research. In particular, the understanding of tissue-specific functions of the GC-GR pathway has been proven to be of substantial value for the identification of novel therapeutic options in the treatment of severe metabolic disorders. Therefore, this review focuses on the role of the GC-GR axis for metabolic homeostasis and dysregulation, emphasizing tissue-specific functions of GCs in the control of energy metabolism.

### ***Introduction***

Secretion of GCs by the adrenal cortex is under control of a prototypic 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 CRH, secretion of the POMC-encoded adrenocorticotrophic hormone (ACTH) and the ACTH-induced stimulation of adrenal GC synthesis. GCs, in turn, inhibit CRH gene expression and

secretion at the hypothalamic level, and interfere with POMC transcription and ACTH-secretion in the anterior pituitary [1-6], thereby establishing a regulatory feedback loop.

At the cellular level, GCs mediate their physiologic effects through binding to a specific, intracellular receptor, the glucocorticoid receptor (GR), which exists as two isoforms. The GR represents a member of the hormone receptor subclass of the nuclear receptor superfamily of transcription factors. Upon GC binding in the cytosol, the GR is released from a heat shock protein (HSP) 90-containing, inactive complex and translocates into the nucleus where it serves as a DNA sequence-specific transcriptional regulator of distinct GC-responsive target genes [7]. GR knock out 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 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 [8].

Main biological functions of the GC-GR axis include, among others, the suppression of inflammation as well as the control of energy metabolism, the latter of which represents the focus of the current article.

### ***Hormonal regulation of metabolism***

Under normal conditions, the pancreatic  $\beta$ -cell hormone insulin triggers the fast uptake and oxidative catabolism of glucose in liver, muscle, and adipose tissue, and simultaneously inhibits glycogenolysis and gluconeogenesis in liver during feeding [9,10]. All of insulin's actions are mediated through its membrane-bound receptor, a member of the tyrosine kinase receptor family [11]. Upon insulin binding, the intrinsic tyrosine kinase activity of the insulin

receptor at the cell surface becomes activated and leads to the subsequent tyrosine phosphorylation of multiple signaling components, thereby transducing the insulin signal to downstream cytoplasmic and nuclear effectors [11-16]. Insulin signal transduction then exerts control over biochemical pathways through either modulation of metabolic key enzyme activities, or through the stimulation or inhibition of metabolic target gene transcription [9,11,17].

Low plasma glucose levels during fasting and exercise trigger a series of hormonal cues that promote a switch in whole body energy usage. Along with a drop in insulin levels, counter-regulatory hormones gain metabolic control. The peptide hormone glucagon from  $\alpha$ -cells within the pancreatic islets and, in particular, adrenal GCs are released into the circulation [18-21], antagonizing anabolic insulin actions [10].

### ***Conditions of elevated GC levels***

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 [18,22-25]. This is most dramatically exemplified by states of either endogenous or exogenous GC deficiency or excess, e.g. Addison's disease, Cushing's syndrome, or GC therapy, 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 [26].

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, fatty liver development, hypertension, elevated cholesterol, immunodeficiency, and insulin resistance [27]. Similar features represent typical side-effects of long-term systemic GC treatment during anti-inflammatory and immunosuppressive therapy [28-30].

Remarkably, many of the aforementioned complications of GC excess represent also prototypical components of the so-called Metabolic Syndrome, which describes an array of closely associated metabolic disorders, such as obesity, hyperglycemia, dyslipidemia, hypertension, and insulin resistance. This metabolic condition is commonly associated with obesity, aging, a sedentary lifestyle, and a genetic predisposition [31], thereby, promoting the susceptibility to severe end-stage diseases such as type II diabetes, atherosclerosis and cardiovascular complications [10].

In the Metabolic Syndrome, the underlying cause for the manifestation of hyperglycemia and dyslipidemia is the development of peripheral resistance against insulin action and the concomitant chronic dominance of its counter-regulatory hormones, in particular GCs. Indeed, GC levels have been found to be elevated in insulin-resistant patients and are strongly associated with a hyperglycemic and fatty liver phenotype [32-34]. In contrast, obesity seems to be not necessarily linked to elevated systemic levels of GCs, but rather displays enhanced local GC action (see below). In addition to the Metabolic Syndrome, chronically elevated GC levels have been identified in patients suffering from a severe wasting syndrome in the tumor-bearing state, e.g. cancer cachexia. In the cachectic state, massive and uncontrolled loss of adipose tissue and skeletal muscle mass lead to a life-threatening weakening of these patients, substantially decreasing life quality, prognosis and tolerance to therapeutic interventions. As a result, roughly 30% of all patients diagnosed with cancer ultimately die of cachexia, underscoring the clinical relevance of this disorder [35-38]. In addition to the Metabolic Syndrome and cancer cachexia, dysfunctional GC action has been described in septic patients

[39,40], thereby, broadening the spectrum of metabolic complications associated with aberrant GC levels.

To this end, metabolic dysarrangements under these pathophysiological conditions reflect impairments of tissue-specific GC activity in metabolically active organs, in particular liver, adipose tissue, skeletal muscle and pancreatic  $\beta$ -cell.

### ***Cell/Tissue-specific functions of GCs and their impact on metabolic diseases***

#### **Liver**

The liver serves as a key relay station in the control of mammalian glucose and lipid homeostasis [41]. Genome-wide analysis of GC-regulated target gene networks has shown that the GR controls many aspects of hepatic energy metabolism, in particular protein and sugar homeostasis. More than 50 genes seem to be direct, regulatory targets of GC action. In many cases the GR functionally interacts with other transcription factors to control specific genetic networks in the liver [42], among which only few have been characterized in detail to date.

One of the prominent features of liver metabolism is the ability for *de novo* glucose synthesis, gluconeogenesis, during fasting in order to provide glucose for extrahepatic tissues such as erythrocytes, renal medulla, and brain [43]. During fasting, free fatty acids or amino acid precursors are channelled into the gluconeogenic pathway that comprises various biochemical steps converting pyruvate to glucose. Main regulatory enzymes are pyruvate carboxylase (PC), which converts pyruvate into oxaloacetate, phosphoenolpyruvate carboxykinase (PEPCK) promoting the decarboxylation of oxaloacetate to phosphoenolpyruvate, and,



finally, glucose-6-phosphatase (G6Pase), hydrolysing glucose-6-phosphate into free glucose and inorganic phosphate [10,44-47].

#### *GCs and hepatic glucose metabolism*

Uncontrolled gluconeogenesis contributes significantly to hyperglycemia in type II diabetic patients [43], the effect of which largely relies on aberrant induction of gluconeogenic gene expression [48,49].

Consistent with a critical role of the hepatic GC-GR axis for systemic blood sugar levels and the development of the Metabolic Syndrome, mice carrying a liver-specific mutation of the GR gene display fasting hypoglycemia and are protected against streptozotocin-induced hyperglycemia [50]. These effects are accompanied by a down-regulation of gluconeogenic enzyme genes upon GR ablation [50], suggesting a causal role of the GR for the induction of gluconeogenesis under insulin-resistant, diabetic conditions. Indeed, liver-specific GR antagonism by antisense oligonucleotides or synthetic compounds is sufficient to cause substantial improvement of hyperglycemia and dyslipidemia in animal models of type II diabetes [51-54]. Also, the GR itself has been found to be over-expressed in hepatocytes of diabetic rodent models, in particular in its nuclear, active fraction [55,56], further substantiating the notion that the GC-GR axis plays a critical role in determining hepatic glucose output via its regulatory function for the promoter activity of gluconeogenic enzyme genes. Consistently, 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 [57].

Recent studies suggest that part of the GC-induced insulin resistance, glucose intolerance and also hypertension depends on the activity and presence of nuclear receptor peroxisome proliferator-activated receptor (PPAR)  $\alpha$ , as GC-triggered hyperglycemia, hyperinsulinemia, and hypertension in wild-type animals were not observed in PPAR $\alpha$  knock out mice.

Interestingly, afferent fibers of the vagus nerve seem to be required for this effect: Selective vagotomy interfered with hepatic PPAR $\alpha$  expression and consecutively diminished GC-induced hepatic insulin resistance and hyperglycemia [58,59].

#### *Molecular control of gluconeogenic enzyme expression*

PEPCK is considered to be the rate-limiting step in the gluconeogenic pathway. Under normal conditions, expression of the cytosolic form of PEPCK is induced in response to fasting via glucagon and GCs, whereas a carbohydrate-rich meal and the concomitant increase in plasma insulin levels acutely decrease its synthesis rate. The hormonal counter-regulation of PEPCK gene transcription by glucagon, acting through cyclic adenosine monophosphate (cAMP), and GCs on the one hand, and insulin on the other has been established as the major regulatory axis for PEPCK activity in response to the fasting to feeding transition [44,60-67].

Following the initial characterization of a glucocorticoid response unit (GRU) within the PEPCK promoter region [68], numerous studies have elucidated the molecular mechanisms by which GCs coordinate the proper response of PEPCK gene expression to hormonal cues. The GRU within the PEPCK gene promoter consists of an array of transcription factor binding sites for the GR itself and additional, so-called accessory factors (AF1 – AF3), all of which are necessary for a full response to GC hormones as mainly demonstrated by mutational analysis and genetic re-constitution studies [68,69] (Fig. 1). Among these, the most prominent factors have been identified as hepatocyte nuclear factor 4 (HNF-4), PPAR $\gamma$ 2, retinoic acid receptor (RAR)  $\alpha$ , retinoid X receptor (RXR)  $\alpha$  (AF1), chicken ovalbumin upstream promoter transcription factor (COUP-TF) (AF1 and AF3) [69-73] as well as forkhead transcription factor FOXO1 and hepatocyte nuclear factor 3 (HNF-3) (AF2) [74-78]. In this setting, the two intrinsic GR binding sites, GR1 and GR2, do not confer GC responsiveness to a heterologous promoter, demonstrating the requirement of a close functional interaction with their accessory factors on the PEPCK gene [79]. In fact, accessory

sites AF1 and AF2 have been shown to create a high-affinity GR binding environment, thereby raising the otherwise low affinity of the GR to the non-canonical GR1 and GR2 sites [80]. More recently, a further extension of the original GRU has been proposed including more distal accessory sites (dAF1 and dAF2) bound by HNF-4 or PPAR $\alpha$  and FOXO1, respectively [81]. The GR interacts with several non-steroid receptors in this context, resulting in a synergistic response of the PEPCK gene to GC exposure [81,82]. The necessity of distinct protein domains within HNF-4 and HNF-3 along with a proper alignment of corresponding recognition sites within the GRU [83] suggests that the control of hepatic glucose metabolism through GCs substantially relies on the specific recruitment of distinct co-activator/co-repressor complexes to the GRU.

Indeed, HNF-4, COUP-TF as well as HNF-3 have been found to commonly interact with the p160 transcriptional co-factor steroid receptor co-activator 1 (SRC-1), which can fully account for the GC-responsiveness of PEPCK gene transcription in genetic re-constitution studies. SRC-1's effect on PEPCK still requires the presence of the GR, which is probably also explained by direct protein-protein interaction [84,85]. Furthermore, combined treatment of hepatocytes with GCs and retinoic acid promotes the recruitment of additional transcriptional co-factors apart from SRC-1, including the acetyltransferases p300/CREB binding protein (CBP) and p300/CBP/cointegrator-associated protein (p/CIP). Ablation of p300 expression in isolated hepatocytes strongly diminishes PEPCK activity, supporting the critical role of histone-modifying co-factors for hormone-inducible PEPCK gene expression [86].

One of the most critical factors for GRU-dependent PEPCK gene expression and its dysregulation in type II diabetes and obesity, has been identified as nuclear receptor co-factor peroxisome proliferator-activated receptor co-activator 1 $\alpha$  (PGC-1 $\alpha$ ). PGC-1 $\alpha$  has been originally cloned as a co-activator for nuclear receptor PPAR $\gamma$  in brown adipocytes, responsible for the tissue-specific induction of thermogenesis in response to cold-exposure

and  $\beta$ -adrenergic signaling [87]. Subsequent studies identified PGC-1 $\alpha$  as a co-activator for multiple nuclear receptors in various cell types [78,88,89], including the GR [90,91].

During fasting, hepatic PGC-1 $\alpha$  is activated in response to catecholamine and glucagon stimulation via a direct cAMP/cAMP responsive element binding protein (CREB) mediated effect on its gene promoter [92]. PGC-1 $\alpha$  then, in turn, mediates activation of the gluconeogenic program including PEPCK in response to GC signals through direct interactions with the GRU-binding transcription factors, GR and HNF-4 via its conserved LXXLL nuclear receptor interaction domain [92-95]. Apart from the induction of PGC-1 $\alpha$ , CREB mediates cAMP-dependent as well as basal PEPCK promoter activity via a consensus cAMP-responsive element (CRE) located at around -100 bp relative to the transcription start site [44,96-98]. Importantly, this CRE site is required for the full GC response of the PEPCK promoter and has been described as an essential accessory site for GR action [99]. It is tempting to speculate that the synergistic activation of PEPCK expression by glucagon/cAMP and GCs relies on the cAMP-dependent induction of nuclear receptor co-factor PGC-1 $\alpha$  and the simultaneous activation of PEPCK transcription via the CRE [92,98,100-103].

In addition to PEPCK, PGC-1 $\alpha$  has been also shown to induce other gluconeogenic genes, in particular G6Pase [88]. Catalyzing the conversion of glucose-6-phosphate to free glucose, G6Pase represents the final step within the gluconeogenic pathway and, at the same time, also controls hepatic glucose release from glycogenolysis [104]. Consistently, disruption of G6Pase activity leads to severe hypoglycemia [48]. Expression of the G6Pase catalytic subunit gene has been known for decades to be induced by GCs: Adrenalectomy disrupts G6Pase expression [105], whereas GC treatment of isolated hepatocytes leads to G6Pase mRNA induction, the effect of which is mediated by the immediate 5'-flanking region of its gene [106-110]. Indeed, three functional GR response elements (GREs) have been identified

within the first 200 bp of the G6Pase promoter [110,111]. Interestingly, the GR seems to functionally cooperate with additional factors in this context, including HNF-1, HNF-4, and FOXO1, all of which are required for the full GC response of the G6Pase promoter [110-112]. Intriguingly, HNF-4 and FOXO1 have been found to be co-activated by PGC-1 $\alpha$  on the G6Pase promoter [88,94], substantiating the notion that the PGC-1 $\alpha$  co-activator represents a master-regulator of the gluconeogenic program.

The fact that PGC-1 $\alpha$  is over-expressed in diabetic db/db mice and functionally contributes to fasting hyperglycemia and insulin resistance in these animals is consistent with the critical role of the GRU (PEPCK)/GRE (G6Pase) and the GC-GR axis in this phenotype [49].

Apart from a direct, activating effect of GCs on increased hepatic glucose output during diabetes, the loss of insulin-dependent repression of PEPCK and G6Pase gene expression substantially promotes hyperglycemia under insulin-resistant conditions [9]. To this end, a defective insulin response in liver has been shown to importantly contribute to the loss of peripheral insulin sensitivity [113-115]. Mice bearing a targeted disruption of the insulin receptor gene in liver display hyperglycemia, hyperinsulinemia, and impaired glucose tolerance [116]. The mechanisms of insulin-mediated PEPCK gene repression are still not fully understood. However, recent evidence suggests that the GR/GRU might also play an important role in this context. Treatment of isolated hepatocytes with insulin leads to the disruption of the GR-associated transcriptional complex on the PEPCK promoter and the manifestation of a repressed, epigenetic promoter status [117]. Also, insulin was demonstrated to directly interfere with GR-mediated transcription, the effect of which was dependent on the GR ligand-binding domain [118]. Furthermore, the atypical nuclear receptor small heterodimer partner (SHP) has been shown to interfere with the GR pathway, thereby, repressing PEPCK gene transcription. This effect of SHP seems to rely on the competition with PGC-1 $\alpha$  for GR and HNF-4 binding, and induction of GR re-localization to the cytosol

[119,120]. Also, direct physical interaction with hepatocyte nuclear factor 6 (HNF-6) also inhibits GR transcriptional activity on the PEPCK gene promoter [121].

Thus, these studies prompt the assumption that not only over-activity of the GR might contribute to aberrant PEPCK expression in type II diabetes but that the GR could also serve as an inhibitory target of insulin or related regulatory pathways, thereby providing a potential check point in the control of liver glucose metabolism under normal or insulin resistant conditions.

#### *GCs and hepatic lipid metabolism*

Apart from hyperglycemia, aberrant hepatic fat accumulation (“fatty liver”, hepatic steatosis) represents a pathophysiological hallmark of the Metabolic Syndrome and is tightly associated with insulin resistance, obesity, glucose intolerance and hypertension [122-125]. Indeed, hepatic fat accumulation directly impairs intracellular insulin signaling by promoting the activation of protein kinase C (PKC) and jun N-terminal kinase 1 (JNK1) pathways, which lead to decreased tyrosine phosphorylation of insulin signaling components downstream of the insulin receptor, such as insulin receptor substrates 1 and 2 (IRS1/2) [126,127]. Consequently, pathophysiological accumulation of lipids in the liver has been identified as an independent risk factor for insulin resistance and the Metabolic Syndrome [128-130].

Chronically elevated GC levels have been intrinsically tied to fatty liver development, and might, therefore, importantly contribute to the hepatic steatosis as observed in the Metabolic Syndrome [18,131-133]. In this respect, hepatic fat accumulation has been demonstrated in patients with Cushing’s syndrome [134,135], and GC levels have been found to be dramatically increased in various animal models of obesity, dyslipidemia, and hepatic steatosis, such as the db/db, ob/ob, and KKA(y) mouse [136,137]. Indeed, treatment of rats with GCs leads to increased triglyceride synthesis, decreased fatty acid oxidation, and to the subsequent accumulation of lipids in the liver [138]. Intracytoplasmatic triglyceride

accumulation can also be observed in isolated hepatocytes when exposed to GCs [139,140]. Consistently, adrenalectomy in rats substantially inhibits hepatic triglyceride accumulation, in particular in response to a high fat diet, the effect of which can be readily reversed by GC replacement therapy [141]. Interestingly, modulation of local glucocorticoid concentration by 11- $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ HSD1) has also been linked to hepatic lipid metabolism. There are two isozymes of 11 $\beta$ HSD that interconvert active cortisol and inactive cortisone. Type 1 is predominantly reductive, thus promoting local regeneration of cortisol, while type 2 resembles the oxidative isozyme catalyzing the inactivation of cortisol [142,143]. The role of 11 $\beta$ HSD enzymes in the regulation of metabolism and their emerging potential as drug targets in glucocorticoid-related disorders has been extensively reviewed elsewhere [24,144]. Nevertheless, hepatic overexpression of 11- $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ HSD1), and the subsequent elevation of local GC levels is sufficient to trigger mild insulin resistance, hepatic steatosis and increased hepatic lipid synthesis/flux. Associated with hepatic 11 $\beta$ HSD1 over-expression and lipid accumulation, expression levels of nuclear receptors LXR $\alpha$  and PPAR $\alpha$  have been found to be elevated in these animals. The fact that these transgenic mice are not obese points to a liver-autonomous role of the GC-GR axis in the control of hepatic lipid metabolism and steatosis [145,146]. Indeed, mice bearing a liver-specific disruption of the GR display diminished hepatic triglyceride levels [147], further arguing, at least in part, for a liver-specific, cell-type-dependent function of the GC-GR pathway in fatty liver phenotypes (Fig. 1).

However, in contrast to the well-defined molecular pathways governing hepatic glucose homeostasis, metabolic and molecular mechanisms of GC-dependent fatty liver development remain largely elusive. GC treatment of isolated hepatocytes was found to enhance the lipogenic capacity of these cells, and to simultaneously increase very low density lipoprotein

(VLDL) production and secretion. These effects most likely reflect the induction of key lipogenic enzyme activities, e.g. acetyl-CoA-carboxylase (ACC) or fatty acid synthase (FAS), and the parallel promotion of VLDL assembly and secretion by hepatocytes [148-152]. In addition, GCs also have been shown to inhibit mitochondrial fatty acid  $\beta$ -oxidation [153], thereby, further promoting intracellular lipid accumulation and a pro-steatotic effect upon long-term GC treatment.

On the molecular level, only isolated target genes of GC action in lipid-metabolizing pathways have been identified to date: GCs are responsible for the increase in apolipoprotein AIV (ApoAIV) expression during fasting, as demonstrated by the loss of ApoAIV induction upon adrenalectomy and its restoration upon GC substitution. However, a direct involvement of the GR could not be demonstrated in this setting [154]. In addition, GCs have been shown to increase the rate of synthesis and secretion of apolipoprotein AI (ApoAI), the effect of which depends on direct ApoAI promoter regulation through the GR [155,156]. Patients receiving GC treatment have elevated levels of ApoAI and its major associated lipoprotein complex, high density lipoprotein (HDL). This potentially beneficial effect of short-term GC exposure is counteracted, however, upon long-term GC therapy, in which also VLDL levels increase (see above) [155,157-159].

Taken together, research over the past decades has established a crucial role of the GC-GR axis for the manifestation of severe metabolic complications, such as hyperglycemia or hepatic steatosis, which constitute important components of the Metabolic Syndrome. However, whereas the functional impact of GCs on hepatic glucose metabolism has been analyzed in great molecular detail, major molecular players and mechanisms of GC-dependent lipid metabolism remain to be defined in future research efforts.



## **Adipose Tissue**

Apart from hyperglycemia and dyslipidemia, obesity represents a hallmark of the Metabolic Syndrome, the co-occurrence of which strongly increases the relative risk of morbidities [10]. Animal knock out studies have highlighted the importance of adipose tissue as an endocrine organ involved in the maintenance of glucose homeostasis and energy balance, and thereby in the pathophysiology of the Metabolic Syndrome [160]. Notably, excessive GC levels as observed in Cushing's syndrome have been identified to be instrumental for the obesity in these patients [24]. Indeed, hyperactivity of the HPA axis is positively correlated with the Metabolic Syndrome as demonstrated in subjects with glucose intolerance, hypertension, and insulin resistance [32,34,161,162], suggesting a causative role for GCs in the obese phenotype. Consistently, treatment of obese rats with the GR antagonist RU486 or adrenalectomy reverse the obese phenotype in these animals [163,164].

In this respect, it is worth mentioning that in particular the occurrence of central (abdominal) obesity has been linked to insulin resistance [165,166]. Consistent with an involvement of the GC-GR axis in this phenotype, also Cushing's patients are characterized by a re-distribution of body fat from the periphery to central/abdominal depots [27,167], which seem to represent GR dense fatty tissue compartments that are in particular sensitive to GCs in obese patients [168-170].

### *Lipolytic functions of GCs*

GCs differentially impact distinct fat depots (Fig. 2): Whereas GCs increase lipolysis by inducing hormone-sensitive lipase [171] 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 [172-174] as well as decreased thermogenesis and uncoupling protein 1 (UCP-1) expression in brown adipose tissue [175].

As the increase in triglyceride breakdown and release of free fatty acids (FFA) play a key role in the attenuation of insulin action in liver and muscle [10], GCs are likely to directly influence systemic insulin sensitivity by virtue of their regulatory function for adipose tissue metabolism.

In this respect, GCs have also been shown to directly influence adipocyte insulin sensitivity by interfering with components of the insulin signaling cascade. GC treatment leads to a down-regulation of IRS1 and IRS2 proteins, blunting intracellular insulin signal transduction [176]. Additionally, phosphoinositide 3 (PI3) kinase activity as well as Akt phosphorylation as markers of insulin signaling strength represent negative targets of GC action in rat adipocytes [177,178]. The inhibitory effect on post-receptor insulin signaling is then also translated into impaired glucose uptake by the glucose transporter 4 (Glut4). Insulin-stimulated re-location of Glut4 to the plasma membrane is efficiently inhibited by GC exposure [179-182], representing a physiological rationale for GC-induced glucose intolerance and hyperglycemia as hallmarks of the Metabolic Syndrome. Consistently, adipose-specific ablation of Glut4 leads to impaired glucose tolerance and insulin sensitivity in mice [183].

PEPCK does not only play a prominent role in hepatic gluconeogenesis but also represents a key enzyme in the glycerogenic pathway in adipocytes. Glyceroneogenesis, the *de novo* synthesis of 3-glycerophosphate from pyruvate and amino acids, provides essential precursors for triglyceride synthesis in this cellular context [184]. Transgenic overexpression of PEPCK specifically in adipose tissue leads to increased adiposity based on enhanced re-esterification of free fatty acids within this tissue [185], the effect of which is further aggravated by feeding the animals a high fat diet [186]. In contrast to the liver, GR negatively regulates PEPCK gene expression in adipocytes by interfering with the activity of the pro-glycerogenic transcription factor CCAAT/enhancer binding protein (C/EBP) [187,188] and the pro-glycerogenic actions of PPAR $\gamma$  and  $\alpha$  ligands, thiazolidinediones and fibrates, respectively [189]. GCs, thereby,

essentially inhibit adipose fat storage and reduce adipose tissue size, which is consistent with the reduced adipose size in animals bearing an inhibitory mutation within the PEPCK promoter region [190].

#### *Pro-adipogenic functions of GCs*

In contrast to insulin resistance, obesity as such (e.g. obesity without diabetes) is not associated with increased systemic levels of GCs, but rather with lower circulating GCs [143]. This seemingly paradoxical finding has been resolved in recent years by studies exploring the function of GC-metabolizing enzymes, e.g.  $11\beta$ HSD, which have been shown to essentially increase local tissue levels of GCs [142]. To this end,  $11\beta$ HSD1 knock out animals display impaired induction of gluconeogenic genes in the liver in response to fasting along with reduced plasma triglyceride levels and enhanced fatty acid oxidation, all of which is consistent with a diminished GC regeneration on a tissue-specific basis. When investigated on an obesity-prone genetic background,  $11\beta$ HSD1-deficient mice are further protected against diet-induced obesity [164,191-193]. Furthermore, transgenic mice over-expressing  $11\beta$ HSD1 specifically in adipocytes show a significant increase in abdominal fat depots, whereas peripheral fat is less affected. This is particularly remarkable since the transgene is expressed in all different types of fat depots [194]. Correlating with this phenotype, adipose-specific elevation of GC levels in these mice leads to the manifestation of all major phenotypes of the Metabolic Syndrome, such as abdominal obesity, glucose intolerance and hypertriglyceridemia. Furthermore,  $11\beta$ HSD1-overexpressing mice are characterized by adipocyte hypertrophy, which is accompanied by decreased levels of the insulin-sensitizing adipocytokine adiponectin and increased local and systemic levels of tumor necrosis factor (TNF)  $\alpha$ , a marker of insulin resistance [194-197].

In addition to adipocyte hypertrophy as observed in this model, GCs promote pre-adipocyte differentiation in primary and cell culture models [198]. This effect is, at least in part, mediated by a non-transcriptional function of the GR, which targets a specific histone deacetylase 1 complex for degradation by the 26 S proteasome, thereby enhancing the expression of critical pacemakers in the cellular differentiation process, e.g. transcription factor C/EBP $\alpha$  [199]. Also, activation of GR by elevated 11 $\beta$ HSD1 levels in isolated adipocytes seems to also co-operate with the PPAR $\gamma$ -dependent adipogenic program to differentiate pre-adipocytes into mature lipid-laden cells. This effect, at least in part, relies on the GR-mediated transcriptional induction of PPAR $\gamma$ 2, a critical checkpoint in the adipogenic differentiation program [200,201]. Furthermore, the GR also associates with transcription factor signal transducers and activators of transcription (Stat) 5a, which, in turn, promotes adipocyte differentiation [202].

Together with the fact that 11 $\beta$ HSD1 expression levels have been found to be increased in obese humans as well as animals [164,203], these studies strongly suggest that local hyperactivity of the GC-GR axis in abdominal adipose tissue critically contributes to the manifestation of the Metabolic Syndrome by functionally cooperating with a variety of other transcriptional regulators and co-factor complexes (Fig. 2). Selective inhibition of 11 $\beta$ HSD1 activity has, therefore, emerged as a novel concept in the treatment of the Metabolic Syndrome and associated disorders [204,205].

## **Skeletal muscle**

### *GCs and muscle catabolism in different metabolic conditions*

A common feature of Cushing's syndrome and steroid therapy is the development of muscle atrophy (steroid myopathy) as a symptom or side effect, respectively [30]. This fact represents

a clear proof for a direct or indirect catabolic effect of excess GCs on skeletal muscle. The biological significance of such effect lies in the altered regulation of metabolism under conditions of stress. Thus, during fasting periods, infection or cancer, when the energetic and substrate requirements of the organism are increased, muscle tissue, constituting 40% of total body mass, is a rich source of amino acids. They can be mobilized and serve as substrates for energy generation, gluconeogenesis and protein synthesis. On the other hand, inhibition of glucose utilization in muscle in response to GCs increases the availability for other tissues, e.g. brain, immune system and tumor.

Skeletal muscle metabolism and the balance between hypertrophy and atrophy are controlled by the action of counter-regulatory anabolic and catabolic signals. In general, contractile activity, nutritional status and the presence of disease/injury determine the type and intensity of signals impinging on muscle tissue [206]. As described in detail below, the insulin/insulin-like growth factor 1 (IGF-1) pathway represents a major anabolic pathway in muscle [207], which is counteracted by GCs. A disturbed balance of counter-regulatory signals under pathological conditions leads to muscle atrophy and its negative consequences.

As described above, increased levels of GC activity are associated with fasting, stress and several metabolic diseases. The question rises as to how important are GCs in the induction of muscle atrophy under such conditions. Steroid myopathy, which is associated with marked atrophy of proximal muscles and mainly fast-twitch type IIB fibres, highlights the potential of GCs as catabolic hormones [30]. Experiments on adrenalectomized rats demonstrated an involvement of GCs in the induction of ubiquitin-mediated protein degradation in muscle during starvation [208].

Insulin resistance in skeletal muscle is associated with the Metabolic Syndrome and has been suggested to promote the development of type II diabetes [10]. Concerning a role of GCs in this process, conclusions from studies on individuals affected by the Metabolic Syndrome are mainly of correlative nature. Nevertheless, GR expression in skeletal muscle of diabetic

patients correlates with the degree of insulin resistance with normalization of GR levels following treatment [209]. Interestingly, mRNA expression of 11 $\beta$ HSD was found to be increased in cultured myotubes derived from muscle of diabetic (type II) patients [210]. A similar observation was made earlier by Whorwood et al. [211]. Thus, increased levels of GR or intramuscular cortisol levels through elevated 11 $\beta$ HSD expression could translate into increased sensitivity of muscle to GCs in affected individuals.

Although GC levels are generally found to be normal in obese individuals [143], elevated corticosterone production was measured in obese *db/db* mice [212]. In this model, insulin resistance and increased GC production were associated with muscle atrophy. Functional conclusions could be drawn from adrenalectomized obese *ob/ob* mice. The absence of adrenal GCs resulted in improved muscle insulin sensitivity and increased protein synthesis [213,214]. Furthermore, insulin resistance in hind limb muscles induced by high-fat diet in rats was ameliorated by treatment with the GC antagonist RU486 [215]. Taken together, increased GC levels or sensitivity in muscle have been associated with conditions related to the metabolic syndrome in several studies and models.

A question of great interest lies in the triggers inducing enhanced GC production and local sensitivity in obesity and the metabolic syndrome. In the case of infection and sepsis, the HPA axis is stimulated by pro-inflammatory cytokines resulting in increased levels of circulating GCs [216]. Amino acid mobilization from muscle during acute infection may be beneficial for the initial response of the organism, however, in severe and prolonged disease muscle wasting and the associated fatigue can become a serious clinical problem. The role of GCs in muscle breakdown was demonstrated in a rat model of sepsis [217]. Treatment of septic rats with the RU38486 antagonist resulted in marked inhibition of muscle protein degradation, in particular through the ubiquitin-mediated pathway. The finding that a strong proportion of proteolysis can be attributed to GC action is remarkable in light of the severe catabolic effects of inflammatory cytokines on muscle during sepsis [218].

A further trigger of GC production is the presence of a tumor. The detection of elevated GC levels in cancer patients with cachexia or tumor-bearing animals was discussed above [36-38]. Although the involvement of GCs in the pathogenesis of cancer cachexia remains elusive, multiple reports from animal models exclude a critical role for this factor. Thus, despite a correlation of GC levels with muscle wasting in different models of cancer cachexia, treatment with RU486 had no effect on the phenotype [219,220]. Similarly, adrenalectomy did not improve wasting in cachectic tumor-bearing mice displaying hypercortisolemia [221].

In conclusion, a broad range of evidence supports the notion that elevated GC activity contributes to muscle catabolism and insulin resistance in several metabolic disorders. However, elucidation of the precise function of GR signaling in muscle during metabolic dysregulation will require generation and analysis of mice with muscle-restricted ablation of the GR gene.

#### *Effects of GCs on glucose and protein metabolism: Molecular pathways*

Although a broad understanding of the effects of GCs on muscle physiology has not been achieved yet, decades of research lead to the conclusion that GCs are able to effectively modulate glucose and protein metabolism in skeletal muscle (Fig. 3). On one hand, GCs inhibit glucose uptake and glycogen synthesis. On the other hand, they suppress protein synthesis while promoting protein degradation and amino acid export. Interestingly, these cellular processes are regulated by the insulin/IGF-1 signaling pathway [207,222]. Of central importance is the activation of Akt kinase, which is mediated by increased IRS1 phosphorylation and PI3 kinase activity downstream of insulin/IGF-1 receptors. Akt promotes glucose utilization and protein synthesis and inhibits protein degradation via multiple downstream pathways. In this context, it is not surprising that GCs exert their catabolic effects on muscle in part by counteracting IGF-1/insulin/PI3-kinase/Akt signaling. This cross-talk can occur at several levels. The ability of GCs to inhibit ligand-induced insulin receptor (IR)

phosphorylation has been a matter of controversy. However, Giorgino et al. could show that treatment of rats with the GR agonist dexamethasone (Dex) leads to reduced IR phosphorylation in skeletal muscle [223]. In a similar experiment, Dex treatment resulted in a reduction of PI3 kinase activity [224]. Akt phosphorylation/activation was inhibited by Dex both, in rat muscle in response to insulin [225] and in cultured C2C12 myotubes [226].

Specific mechanisms by which GCs influence glucose metabolism in muscle have been described in detail. Thus, a central aspect of GC-induced insulin resistance in muscle resides in the suppression of glucose uptake mainly through inhibited translocation of the glucose transporter Glut4 to the cell surface (Fig. 3) [180,227]. Furthermore, GC treatment results in reduced glycogen synthesis through a mechanism involving suppression of glycogen synthase activity [228,229]. It is noteworthy that both Glut4 translocation and glycogen synthase activity are positively regulated by Akt [230].

While the involvement of GCs in the induction of insulin resistance is of great interest in respect to the pathogenesis of type II diabetes, regulation of protein metabolism is a major concern in disorders associated with severe muscle atrophy. The availability of free amino acids and Akt signaling represent two pathways regulating protein synthesis (Fig. 3) [222]. The former is influenced by GCs through inhibition of amino acid uptake into muscle cells [231]. The negative effect of GCs on signaling events regulating protein synthesis downstream of Akt was demonstrated in muscle of rats treated with Dex [232]. Reduced protein synthesis was associated with decreased phosphorylation of p70 S6-kinase and eukaryotic Initiation Factor 4E (eIF4E)-binding protein 1, events which would be expected to account for reduced efficiency and inhibited initiation of translation.

A plethora of studies has provided evidence for the enhancement of skeletal muscle protein degradation in response to GC treatment, particularly via the ubiquitin-proteasome pathway. Expression of the E3 ubiquitin ligases atrogin-1 and Muscle Ring Finger 1 (MuRF-1) is



restricted to skeletal muscle and is induced in various types of atrophy [233] as well as in response to Dex [234]. These proteins promote ubiquitination of specific protein substrates, thereby targeting them for proteasomal degradation. Genetic ablation of either gene revealed an essential function during denervation-induced atrophy [234]. Expression of atrogin-1 and MuRF-1 is induced by activation of transcription factors Foxo1 and Foxo3, which is prevented by anabolic signals via the Akt pathway [226,235]. Dex positively regulates E3 ligase expression by inhibiting Akt phosphorylation, thereby permitting activation of Foxo1 and 3. In addition, as shown in mice treated with Dex, GCs are able to induce the expression of both transcription factors in muscle [236]. The notion that GCs promote a general gene expression program driving protein degradation is further supported by reports on increased expression of relevant genes in response to Dex, such as ubiquitin C, proteasome subunits and cathepsin L (lysosomal protein degradation) [237-239]. Finally, the process by which free muscle amino acids are converted to glutamine for export and utilization in other tissues is enhanced by GCs during stress, through the upregulation of glutamine synthase expression [240].

A novel mechanism involved in GC signaling has been uncovered recently. Expression of the secreted protein myostatin, an inhibitor of muscle growth, was found to be increased in response to Dex both, in rat muscle and in C2C12 myotubes [241,242]. Myostatin both suppresses protein synthesis and is able to enhance expression of atrogin-1 and MuRF-1 in skeletal muscle *in vivo* [243,244]. Notably, expression of atrogin-1 in response to myostatin treatment appeared to be dependent on increased Foxo1 expression and activity [243]. The functional significance of GC-dependent myostatin upregulation was confirmed in myostatin gene deficient mice, which were resistant to Dex-induced muscle atrophy [245].

Almon et al. obtained gene expression profiles from skeletal muscle of rats treated with Dex and identified changes in 22 genes associated with the development of insulin resistance [246]. Although functional validation of transcriptional changes remains to be determined,

such approaches will be helpful in order to achieve a more global picture of the molecular mechanisms of GC action in muscle. Furthermore, several questions of central importance await answers. For example, the precise mechanisms by which GCs inhibit the Akt pathway remain elusive. The scarcity of established direct transcriptional targets of the GR in muscle cells is remarkable. It is also unclear whether the catabolic effects of GCs on skeletal muscle are dependent on dimerisation, DNA binding and transactivation by the GR. The finding that Dex-mediated protein degradation in myotubes was dependent on the co-activator p300 implies involvement of transactivation in the regulation of this process [247]. Characterization of muscle metabolism in mice carrying dimerization-deficient GR alleles [8] might give good clues in this direction.

### **Pancreatic $\beta$ -cells**

Glucose intolerance, a phenomenon closely associated with the development of type II diabetes, is a consequence of insulin resistance in liver, muscle and adipose tissue on one hand and failure of pancreatic  $\beta$ -cells to compensate hyperglycemia with increased insulin secretion on the other [10]. Diabetes mellitus frequently occurs during steroid therapy and Cushing's syndrome and has been associated with reduced  $\beta$ -cell insulin secretion [30]. Indeed, it was demonstrated in experiments with cultured  $\beta$ -cells that GCs are able to suppress insulin secretion [248]. Furthermore, it was reported that Dex treatment caused decreased stability and protein levels of the glucose transporter Glut2 and this correlated with an inhibition of glucose-stimulated insulin secretion [249]. Further evidence for the ability of GCs to suppress insulin output was obtained *in vivo* in experiments with mice overexpressing the GR in pancreatic  $\beta$ -cells. This genetic modification leads to decreased insulin secretion accompanied by reduced glucose tolerance in adult mice and hyperglycemia in aged mice

[250,251]. In the latter case, enhanced  $\alpha$ -adrenergic receptor signaling was reported in GR-overexpressing cells, a finding that has been linked to suppression of insulin release [251]. Additional mechanisms contributing to reduced insulin output involve apoptosis [252] and increased K<sup>+</sup> channel activity [253]. Ullrich et al. showed that up-regulation of Serum- and Glucocorticoid-inducible Kinase (SGK1) expression by GCs is necessary for increased activity of K<sup>+</sup> channels, which in turn can account for inhibition of insulin release in  $\beta$ -cells [253].

Taken together, multiple pathways controlling insulin secretion by  $\beta$ -cells are influenced by GCs.  $\beta$ -cell-specific inactivation of GR function under disturbed metabolic conditions could provide direct proof for the significance of such effects in the pathogenesis of glucose intolerance and diabetes.

### Novel GC effectors

Recently, the upregulation of MAP Kinase Phosphatase 1 (MKP-1) and Tribbles-homologue 3 (TRB3) expression by GCs was described [254-256]. Given the involvement of these signaling proteins in the regulation of several metabolic processes these findings could contribute to the dissection of novel pathways modulating metabolism in response to GCs.

MKP-1 is a MAPK phosphatase that is able to inactivate MAPKs, including Erk, JNK and p38, through dephosphorylation of threonine and tyrosine residues [257]. MKP-1 expression was shown to be increased in Dex-treated cells [255,256] as well as in high fat diet-fed mice [258]. The increased susceptibility of MKP-1 null mice to endotoxemia highlights its role in the suppression of inflammatory responses, possibly downstream of GCs [259-262]. Interestingly, MKP-1 knockout mice display a metabolic phenotype [257]. Amongst other phenotypic changes, decreased hepatic lipid content associated with enhanced liver fatty acid  $\beta$ -oxidation was observed. Since excess GC activity can result in liver steatosis and suppression of fatty acid  $\beta$ -oxidation (see above) one could speculate that some of these effects are mediated by induction of MKP-1 expression.

Du et al. showed that expression of TRB3, a mammalian homologue of *Drosophila tribbles*, is induced by Dex in hepatocytes as well as in liver of fasted or diabetic *db/db* mice [254]. Strikingly, hepatic overexpression of TRB3 in wild type animals led to hyperglycemia and glucose intolerance while liver-specific RNAi-mediated knockdown improved glucose tolerance [254,263]. These results could be explained by inhibition of insulin-stimulated Akt signaling as a consequence of direct binding of TRB3 to Akt. The inhibitory interaction between the two proteins could also be demonstrated in skeletal muscle and C2C12 myotubes [264]. In addition, in mice with a muscle-specific disruption of the LKB1 (Serine-Threonine Kinase 1) gene, coding for a kinase upstream of the energy-sensing kinase AMP-activated

protein kinase (AMPK), TRB3 down-regulation in muscle was associated with increased insulin sensitivity [264]. These results imply that TRB3 could be partly responsible for inhibition of the insulin/Akt pathway and emergence of insulin resistance in liver and skeletal muscle in response to GCs. An additional function of TRB3, namely in adipose tissue, could also be relevant to GC action. TRB3 expression is induced in adipose tissue during fasting and TRB3 overexpression resulted in increased fatty acid oxidation and protection of mice against diet-induced obesity [265]. Mechanistically these effects were attributed to specific TRB3-dependent enhancement of ubiquitin-mediated degradation of ACC, the rate-limiting enzyme in fatty acid synthesis. In conclusion, both MKP-1 and TRB3 represent promising candidates as potential mediators of metabolic GC effects. However, their functional involvement in metabolic pathways downstream of GCs remains to be confirmed.

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. Increased systemic oxidative stress could be correlated with obesity in both humans and mice [266,267]. Notably, antioxidant treatment of diabetic/obese subjects has been partly successful in improving insulin sensitivity, glucose and lipid homeostasis [266-268]. Houstis et al. provided direct evidence for an involvement of ROS in GC-induced insulin resistance in adipocytes [268]. 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. 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.

## ***Outlook***

It has been a major objective of this article to describe the plethora of evidence suggesting a causative role of GCs in the development of metabolic disorders. Understanding the precise function of the GR and associated regulatory networks is of great importance for biomedical research. 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 (Fig. 4A) [30]. Despite increased levels of endogenous GCs, septic patients benefit from treatment with low doses of corticosteroids [269]. Similarly, clinical trials have led to the conclusion that short term corticosteroid treatment of cachectic patients with advanced cancer can improve their quality of life [270]. Nevertheless, side effects of steroid therapy remain a great hurdle, and research has focused on the development of so-called ‘dissociated steroids’ [30]. 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 (Fig. 4A) [271,272]. The concept of SEGRAs has been validated through a genetic approach, namely by the analysis of mice expressing dimerization-deficient GRs (GRdim). Thus, although certain activating functions of the GR were abolished, its anti-inflammatory effects were mostly preserved during endotoxemia [8]. Given the involvement of GCs in the pathogenesis of metabolic disorders, could pharmacological interference with GR function have therapeutic potential? 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 (Fig. 4A) [273]. In this respect, discovery of GR ligands that suppress GC-dependent metabolic abnormalities while maintaining anti-inflammatory properties would be of great interest (Fig. 4B).

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

#### *Acknowledgements*

We apologize to our colleagues whose contributions could not be cited due to space limitations. We thank Ulrike Lemke, Ulrike Hardeland, and Mauricio Berriel Diaz for critically reading the manuscript and discussions. Our work is supported by grants from the Deutsche Forschungsgemeinschaft, the Thyssen Foundation, the Novartis Foundation for Therapeutic Research, the European Foundation for the Study of Diabetes, and by a Marie Curie Excellence Grant from the EU commission.

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### **Figure Legends**

**Figure 1: GC/GR-regulated metabolic pathways in the liver.** Aberrant levels of GCs promote hyperglycemia through the induction of gluconeogenic enzyme genes, PEPCK and G6Pase. Schematic representation of the GRU and associated factors/co-factors within the PEPCK gene promoter shown. In addition, elevated GCs promote very-low-density lipoprotein (VLDL) production and secretion as well as triglyceride synthesis via fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC). Along with the inhibition of free fatty acid (FFA)  $\beta$ Oxidation via interference with the activity of Acyl-CoA dehydrogenase (DH), GCs, thereby, trigger hepatic fat accumulation (steatosis) as well as systemically elevated blood lipid levels. Red arrows indicate induction or inhibition of corresponding pathways through the GC/GR axis, respectively.

**Figure 2: Distinct functions of GCs in peripheral and central fat depots.** GCs fulfill antagonizing functions in peripheral and abdominal/central fat depots, respectively, leading to abdominal obesity and insulin resistance. In the periphery, GCs promote lipid breakdown (lipolysis, PEPCK inhibition) and reduced FFA uptake (lipoprotein lipase (LPL) inhibition). In contrast, hypertrophy and differentiation of central adipocytes are enhanced by GCs via the cooperation with PPAR $\gamma$  and C/EBP transcription factors. HSL, hormone-sensitive lipase.

**Figure 3. GC action on skeletal muscle.** GCs regulate glucose utilization and protein turnover via multiple pathways. The physiological processes affected by GCs are displayed in open boxes. Arrows in red indicate GC-mediated actions. The precise mechanisms of signaling downstream of GCs/GR remain unclear for several of the pathways indicated.

**Figure 4. The interrelation of the GR, inflammation and metabolic dysregulation. Implications for pharmacological intervention.** **A.** GCs are potent inhibitors of inflammatory responses. On the other hand, metabolic dysregulation and disease can be mediated by the GC/GR axis. Inflammation can also contribute to insulin resistance and the pathogenesis of the Metabolic Syndrome. **B.** Optimal pharmacological manipulation of the GR would result in efficient and balanced suppression of inflammatory responses with the simultaneous inhibition of GC-mediated metabolic abnormalities.







