Chapter 6
How Do Glucocorticoids Regulate Lipid Metabolism?

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Abstract Glucocorticoids (GCs) and their cognate, intracellular receptor, the glucocorticoid receptor (GR) have been characterized as critical checkpoints in the hormonal control of energy homeostasis in mammals. Whereas physiological levels of GCs are required for proper metabolic control, aberrant GC action has been linked to a variety of severe metabolic diseases, including type 2 diabetes and obesity. As a member of the nuclear receptor superfamily of transcription factors, the GR translocates into the cell nucleus upon GC binding where it serves as a transcriptional regulator of distinct GC-responsive target genes that are in many cases associated with lipid regulatory pathways and thereby intricately control both physiological and pathophysiological systemic lipid homeostasis. Thus, this chapter focuses on the current knowledge of GC/GR function in lipid handling and its implications for systemic metabolic dysfunction.

Keywords Glucocorticoid receptor • Glucocorticoid hormones • Liver • Adipose tissue • Lipid metabolism • Lipoprotein metabolism • Cholesterol metabolism

Lipid Metabolism at a Glance

The maintenance of metabolic homeostasis depends on the highly regulated interaction of nutritional, neural, and endocrine stimuli. The continuous cycle of nutrient acquisition from the ingested food and the depletion of nutrients involves the coordination of several biomolecular processes at all levels of the animal's biology. Each of the major metabolic organs of the body—the liver, muscles, adipose tissues, intestines, pancreas, and the brain—depends on the major food groups of carbohydrates, proteins, and fats to support various physiologic processes of the organism [1, 2].

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Compared to carbohydrates and proteins, lipids, due to their amphipathic or non-polar nature, are digested, absorbed, and processed in the body differently. Lipids in food require emulsification by liver-derived bile salts in the digestive tract to facilitate pancreas-derived lipase action and intestinal absorption. Cholesterol esters and re-formed triglycerides in the intestinal enterocytes are packaged into lipoproteins, the chylomicrons (Fig. 6.1), which drain via the lymphatics before emptying into the blood vessels [1, 2]. Triglycerides in lipoproteins are acted upon by lipoprotein lipases (LPL) which are tethered to the walls of capillaries by proteoglycans and GPIHBP1 [3, 4]. Fatty acid then move into the cells with the help of transport proteins (fatty acid transport proteins, FATP; fatty acid translocase, FAT/CD36; caveolin-1 and fatty acid-binding protein, FABP) [5]. Cholesterol esters inside lipoproteins are transported into the cell via receptor-mediated processes involving the low-density lipoprotein receptor (LDLR), lipolysis-stimulated lipoprotein receptor (LSR), LDLR-related protein (LRP), and the scavenger receptor (SRB1). The majority of the fatty acid transporters are located on the surface of adipocytes, hepatocytes, and muscle cells, while most lipoprotein receptors are expressed by hepatocytes [6].

Apart from chylomicrons, four other types of lipoprotein particles are recognized to be involved in lipid transport (Fig. 6.1). They differ in size and density which

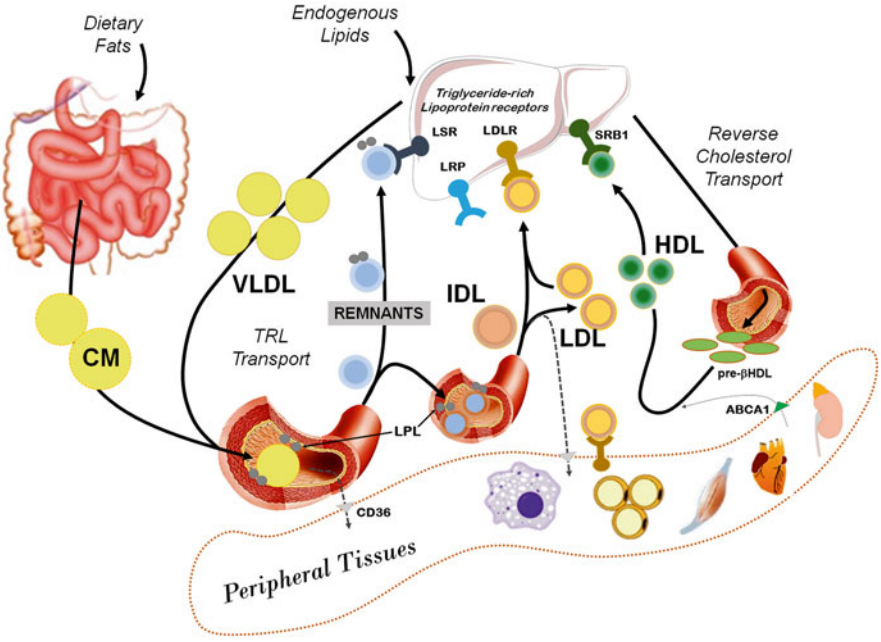

Fig. 6.1 The lipoprotein pathway. *ABCA1* ATP-binding cassette transporter A1, *CM* chylomicrons, *HDL* high-density lipoproteins, *IDL* intermediate density lipoproteins, *LDLR* LDL receptor, *LPL* lipoprotein lipase, *LDL* low-density lipoproteins, *LRP* LDL receptor-related protein, *LSR* lipolysis-stimulated lipoprotein receptor, *SRB1* Scavenger receptor class B member 1, *TRL* triglyceride-rich lipoproteins, *VLDL* very-low-density-lipoproteins

depend on the varying lipid and apolipoprotein contents of each particle [6]. Triglycerides and cholesterol esters comprise the core of the particle while amphipathic phospholipids, unesterified cholesterol, and proteins are found in the outer shell. Apolipoproteins function by activating or inhibiting enzymes important in the transport process and by serving as ligands for cell surface receptors [6]. ApoB and apoE, for example, can be recognized by the LDLR and LSR receptors while ApoCII activates lipoprotein lipase that hydrolyzes triglycerides [7]. Dietary (exogenous) lipids are transported through chylomicrons while endogenous lipids from the liver are transported by very-low density lipoproteins (VLDL) which can give rise to intermediate density (IDL), low-density (LDL), and remnant lipoprotein particles. High density lipoproteins (HDL) are involved primarily in the transport of cholesterol from the peripheral tissues to the liver [2, 6].

The triglycerides and fatty acids being transported from the liver come from different sources: (1) from the chylomicron remnants, (2) *de novo* lipogenic pathway (DNL), and (3) fatty acids from lipolysis in adipocytes [1, 8]. Cholesterol, on the other hand, is provided from (1) the diet via chylomicron remnants, (2) *de novo* synthesis of cholesterol, and (3) from other lipoproteins internalized by the liver [9].

In the cell, fatty acids can be converted into triglycerides or used as source of energy during starvation through mitochondrial β-oxidation. Triglycerides can be packaged into lipoprotein particles (liver) or stored in depots (adipose tissues). In β-oxidation, long-chain fatty acids (LCFAs) are channeled across the mitochondrial membrane, with the help of carnitine palmitoyltransferase-I (CPT-I), and acetyl-CoAs are generated and extracted for energy via the Kreb's cycle and electron transport chain. Fatty acids can also be used for the synthesis of eicosanoids (prostaglandins, thromboxanes, leukotrienes), glycerophospholipids (plasmalogens and phosphatidates), and sphingolipids (sphingomyelin, cerebrosides, gangliosides) [10]. Cholesterol is then used as component of biomembranes and for the synthesis of bile acids (cholic, glycocholic, taurocholic, lithocholic acids), steroid hormones (androgens, progestins, estrogens, glucocorticoids, and mineralocorticoids), and secosteroids (vitamin D) [11].

Insulin and counter-regulatory hormones, which include the glucocorticoids (GCs), play major roles in keeping the balance of metabolites in the cell by activating or deactivating key enzymes involved in different anabolic and catabolic pathways [12]. Furthermore, inter-organ nutrient cross-talk depends primarily on the hormonal signals perceived by the cells. These are true for glucose, amino acid, and lipid metabolism. Below, we present collective information on how GCs regulate lipid metabolism in adipocytes, the liver, and other tissues. Most of the enzymes that are regulated by GCs in lipid pathways are in fact the same ones that are dysregulated in chronic conditions of GC excess i.e. Metabolic and Cushing's syndromes.

GCs and Adipose Tissue

The adipose tissues are the major fat depot of the body. Excess triglycerides that cannot be used by the body as well as excess glucose can be stored as fats in white adipose tissues [2]. Here, triglycerides remain until needed in times of nutrient deprivation.

Abdominal and visceral adiposity are now regarded as an important criteria contributing to the collective dysfunctional phenotypes of the Metabolic Syndrome [13]. Interestingly, this abnormal deposition of fats in the body is likewise observed in Cushings syndrome where the individual suffers from hyperactive HPA axis and hypercortisolemia [14, 15]. However, one key distinction between metabolic syndrome and Cushing syndrome is that patients with Metabolic Syndrome have normal or increased amounts of peripheral adipose and patients with Cushings syndrome typically have decreased peripheral adipose. This partially overlapping phenotype between Metabolic and Cushings syndrome demonstrates potential important role of GCs in adipose tissue physiology.

Effects of GCs on Adipocyte Differentiation

GCs have been reported to possess pro-adipogenic function. This was realized in transgenic mice over-expressing 11beta (β)-HSD1 in adipocytes thus increasing active local GC levels. In these mice, a significant increase in abdominal fat was observed whereas peripheral fats were less affected [16]. Furthermore, the specific elevation of GCs in adipose tissues resulted in the manifestation of major phenotypes of the metabolic syndrome such as abdominal obesity, glucose intolerance, and hypertriglyceridemia. The adipocyte hypertrophic phenotype observed in these animals also results in decreased levels of adiponectin, an insulin-sensitizing adipokine, and increased local and systemic levels of the cytokine tumor necrosis factor-alpha (TNF-α), a marker of insulin resistance [16–19].

Apart from the adipocyte hypertrophic phenotype of mice over-expressing 11β (beta)-HSD1, GCs have been shown to promote differentiation *in vitro* [20]. Cortisol and dexamethasone, a synthetic glucocorticoid, have been widely used as a component of the adipogenic induction cocktail for adipose stromal cells, primary and 3T3-L1 pre-adipocytes [21, 22]. This function of GCs can be attributed to both transcriptional and non-transcriptional action of the GR. The GR has been reported to act on specific histone deacetylase 1 complex for degradation by the 26S proteasome, thus promoting the expression of transcription factors (i.e. C/EBP-alpha (α) and STAT5) necessary for the differentiation process [23, 24]. In primary adipocytes isolated from 11β (beta)-HSD1-over-expressing mice, peroxisome-proliferator activated receptor—gamma (PPARγ), an important regulator of lipogenesis and adipogenesis, has been reported to be up-regulated [25–27]. In other recent reports where the GR function was rendered deficient pharmacologically or genetically [28], adipogenesis was shown to be inhibited *in vitro* which may depend on GR-induced expression of genes such as Krüppel-like factor 15 (KLF15) [29]. Since elevated 11β (beta)-HSD1 activity has been reported in both human and mouse obesity, these are therefore, indicative of the possible contribution of GC/GR signaling in the development of the Metabolic Syndrome by regulating the expression of transcriptional regulators and complexes [30–32].

Effects of GCs on Adipose Tissue Lipolysis

During fasting and starvation, fatty acids and glycerol are release from their storage form as triglycerides in adipose tissue fat depots. Lipases are involved in catalyzing the hydrolysis of the ester bonds between fatty acids and glycerol. Adipose triglyceride lipase (ATGL/desnutrin) hydrolyzes triglyceride into diacylglyceride (DAG) and fatty acid. DAG is in turn hydrolyzed by hormone-sensitive lipase (HSL) into monoacylglyceride (MAG) and another molecule of fatty acid. The final hydrolysis step that completely liberates fatty acids and glycerol is catalyzed by monoglyceride lipase (MGL). Under normal, basal (fasted) physiologic state, GCs promote lipolysis in adipose tissues by inducing activity of all three lipases and reducing LPL activity [33–37]. This lipolytic function of GCs is more pronounce in peripheral adipose than in abdominal depots where adipogenic and lipogenic programs are favored [38, 39]. GCs are also known to induce expression of FoxO transcription factors which are known regulators of the lipases [40, 41].

In addition to the possible direct GR regulation [34] or indirect effects via FoxO, GCs can also affect lipolysis by acting on upstream regulators. Cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA) pathway which is stimulated by catecholamines via G-protein coupled, β (beta)-adrenergic receptor activates HSL and the lipid droplet surface protein perilipin which facilitates fatty acid release by promoting ATGL and HSL function [42, 43]. This process is actually inhibited by insulin via phosphoinositide-3 kinase (PI3K)-protein kinase B (PKB/Akt) signaling which activates the cAMP-hydrolyzing enzyme, phosphodiesterase 3B (PDE3B) [42, 43]. The lipolytic action of catecholamines via beta (β)-adrenergic stimulation occurs rapidly compared to glucocorticoids which takes several hours [44]. It has been postulated that GCs increase intracellular cAMP levels by (1) increasing PKA activity, (2) inhibiting PDE3B expression and/or (3) by inducing expression of angiopoietin-like 4 (ANGPTL4) [44–46].

ANGPTL4 is a hypoxia-induced, secreted glycoprotein that can interact with proteoglycans of the extracellular matrix [47, 48]. It has been reported that GCs promote secretion of ANGPTL4 from the liver and white adipose tissues [49]. ANGPTL4 in turn activates adipose tissue lipolysis and inhibits LPL activity resulting in elevation of free fatty acids in the circulation [50]. Furthermore, ANGPTL4 expression is found to be highly induced during fasting, when the levels of GCs are high, and is inhibited by treatment with RU486, a GR antagonist. [51] Mice lacking ANGPTL4 have reduced fasting-induced WAT lipolysis further demonstrating the possible role of the GC/GR signaling in the process [51]. In line with this, a conserved GRE is present in the rat, mouse, and human ANGPTL4 gene locus [45]. The exact mechanism by which GC-dependent, ANGPTL4-induced lipolysis works remains to be elucidated, but the main hypothesis points to cAMP activation which was observed to be deficient in WAT of ANGPTL4 knockout mice [45]. The importance of this protein in adipose tissue biology, nevertheless, is justifiable as increased ANGPTL4 expression is demonstrated to be associated with elevated fatty acids in both Type 1 and Type 2 diabetes mouse models [52]. This process is also implicated

in fatty acid redistribution from adipose tissue to the liver which in turn increases triglyceride synthesis in hepatocytes [33].

Studies on the lipolytic action of GCs in humans have been largely inconsistent across different steroidal preparations, length of GC administration, distinct fat depots, and characteristics of the study population itself. To mention a few, in Cushing's patients [53, 54] and individuals who received chronic GC treatments [55–57], the rate of non-esterified fatty acid (NEFA) turnover is unaffected. This potential anti-lipolytic activity of GCs is also observed *in vitro* in 3T3-L1 cells treated with high concentration of corticosterone (>1 μM). The effect though, is reversed upon removal of the GC from the medium favoring once more lipolysis [35]. In other studies in humans involving infusion of fatty acid stable-isotope and acute physiological hypercortisolemia, an increase in blood NEFA levels is observed [58, 59]. This is probably due to an increased lipolysis from subcutaneous fat depots when insulin levels were normal [58].

With regards to fatty acid oxidation, there has been no concrete report on how GCs could possibly affect this pathway. Furthermore, no study has examined the role of adipose tissue GR using genetic gain- or loss-of-function models which could further provide insight on how GCs regulate lipid metabolism.

Effects of GCs on *de novo* Lipogenesis and (β)-Oxidation

Fatty acids can be synthesized from non-lipid materials, like glucose, via the de novo lipogenic pathway (DNL). DNL takes place both in the liver and the adipose tissues with synthesized fatty acids stored as triglycerides as cytosolic lipid droplets [60]. In adipocytes, TG is made by successive acylation and dephosphorylation of a glycerol-3-phosphate backbone. Specifically, glycerol-3-phosphate is acylated by GPAT resulting in lysophosphatidic acid which is acylated by AGPAT to form phosphatidic acid. Phosphatidic acid is dephosphophorylated by phosphatidic acid phosphatase, otherwise known as lipins to yield diacylglycerol. In the final step DAG is acylated by DGAT to form triglyceride. There are several isoforms of each enzyme class. Interestingly, some, but not all isoforms are induced by glucocorticoids in mice [34].

In contrast to lipolysis, lipogenesis is activated by insulin in times of nutrient excess. One might expect that in this case, GCs might be inhibitory but experimental evidence said otherwise. Despite the low levels in the fed state, GCs have been shown to potentiate the lipogenic function of insulin by regulating the expression of some genes in the pathway [61]. This synergistic response in lipogenesis is shown to be important also in adrenalectomised rats [62] and human adipocytes [63].

The synthesis of fatty acids from glucose starts with acetyl-CoA, the product of the action of pyruvate dehydrogenase on the final metabolite of the glycolytic pathway. Acetyl-CoA carboxylase (ACC) then converts acetyl-CoA to malonyl-CoA which is in turn the substrate for fatty acid synthase (FASN), a rate-determining enzyme of lipogenesis. GCs have been reported, both *in vivo* and *in vitro*, to regulate the

expression of ACC and FASN [44, 61, 64, 65]. GR-binding regions in or nearby the genes coding for these enzymes have been identified in both mouse and human genome [34, 63, 66]. In one study, mRNA levels of ACC and FASN in a human adipocyte cell line are shown to be induced by GC treatment [64]. The lipogenic program, however, is decreased and could only be increased by addition of insulin which supports previous reports on the GC-insulin synergism [62, 63].

GCs are known to affect the oxidation of fatty acids in both adipose tissues and the liver. In the former, one proposed mechanism is via the induction of expression of Tribbles-homologue 3 (TRB3) by GCs. TRB3 expression is induced in adipose tissues during fasting and over-expression of the protein resulted in increased fatty acid oxidation and protection of mice against diet-induced obesity [67]. In contrast to pro-lipogenic effect of GCs, TRB3 has been shown to promote ubiquitin-mediated degradation of ACC explaining how the oxidative pathway could have been favored [67]. In a similar report but in chronic lymphocytic leukemia (CLL) cells where resistance has been observed with GC treatments [68], dexamethasone is found to induce the expression of PPAR-α (alpha) and δ (delta) [69]. PPARα and δ are known to regulate fatty acid oxidation [70]. Whether the same mechanism works in adipose tissues and the liver remains to be investigated. Nevertheless, all these reports prove that GCs play an important role in the regulation of lipid homeostasis in adipose tissues.

The Hepatic Functions of GCs

The liver is a central metabolic organ involved in the control of mammalian glucose and lipid homeostasis [71]. Genome-wide analysis of GC-regulated target gene networks has shown that the GR controls many aspects of hepatic energy metabolism. 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 [72], among which only few have been characterized.

Control of Hepatic Triglyceride Metabolism and VLDL by GCs

Besides ACC and FASN, other enzymes involved in lipogenesis and TG synthesis have been reported to be regulated by GCs in the liver. Stearoyl-CoA desaturase (SCD1/2), glycerol-3-phosphate acyltransferase (GPAT3/4), 1-acylglycerol-3-phosphate acyltransferase (AGPAT2), lipin 1 (LPIN1), and diacylglyceride acyltransferase (DGAT1/2) are all implicated to be regulated directly or indirectly by the GR [73–75]. As in adipose tissues, GC/GR pro-lipogenic activity in the liver seems to require insulin signaling [74, 76]. This process is possibly important in

the development of hepatic steatosis prior to the onset of insulin resistance in Metabolic Syndrome [8]. Hepatic steatosis is, in fact, a prominent negative side-effect of long-term GCs treatment [39]. In accordance to this, liver specific GR loss-of-function reduces TG levels in normal [77] as well as diabetic [78] mice and reduces accumulation of TG in liver during liver regeneration [28].

Several mechanisms have been proposed on how GCs promote TG synthesis and hepatic steatosis one being the inhibition of the hairy and enhancer of split 1 (HES1) repressor by GCs [78]. GR loss-of-function manipulations in the liver and hepatocytes resulted in up-regulation of HES1 that increases expression of pancreatic lipase (PNL) and pancreatic lipase-related protein (PLRP2), proteins involved in the "lipase arm" of GR-dependent TG metabolism. Both PNL and PLRP2 are repressed by GC-mediated HES1 inhibition thereby explaining hepatic triglyceride accumulation. Furthermore, liver HES1 expression is repressed in mouse models of hepatic steatosis and overexpressing HES1 in these models partially reverses the steatotic phenotype [78]. Another possible mechanism by which GCs control triglyceride turnover in the liver is via carboxyesterase 1d (CES1D/triacylglycerol hydrolase, TGH). TGH is believed to be involved in triglyceride lipolysis of fats droplets in hepatocytes [75]. Just like PNL and PLRP2, TGH mRNA levels are repressed upon dexamethasone treatment which could be explained by GC-induced destabilization of the mRNA at the 3′-UTR [75].

The composite function of the GR in concert with other transcription factors which could be a repressor or activator adds additional layer to the role of GCs in controlling hepatic lipid metabolism. The liver X receptor (LXR), for example, is known to interact with the GR [79] and it has been reported that mice lacking LXR-β (beta) has reduced GC-induced triglyceride accumulation [80]. The same phenotype is observed in mice where MED1 is specifically inhibited in the liver (Med1Δ^{liver}) [81]. MED1 is a co-activator subunit of the Mediator complex which in turn participates in RNA Pol II-dependent transcription [82]. In dexamethasone-treated Med1Δ^{liver} mice, levels of fatty acid oxidation genes—short-chain and medium-chain acyl-CoA dehydrogenase (SCAD & MCAD)—are normalized compared to wild type mice where the genes are repressed by GC treatment [81]. The mechanism could also involve PPARγ which is known to be induced by GCs [27]. In a follow-up study in the same Med1Δ^{liver} mice where PPARγ is inhibited with an adenovirus, mice are protected from high-fat diet induced hepatic steatosis with impaired induction of lipogenic genes, adiponectin, and lipid droplet-associated genes [83].

Apart from potential direct effects on the enzymes of DNL and TG synthesis, GCs can regulate expression of secreted factors that can likewise affect lipid load in hepatocytes. As mentioned above, GCs induce secretion of ANGPTL4 from the liver and adipose tissues. ANGPTL4, with its pro-lipolytic activity, increases NEFA being released in the circulation which can serve as substrate for TG synthesis in the liver. Indeed, ANGPTL4 null mice are protected from GC-induced hepatic steatosis and hyperlipidemia [45]. Another intriguing recent study has shown that osteoblast specific GR knockout reduces the negative metabolic side effects of

chronic GC treatments probably involving the bone secretion of osteocalcin or the bone γ-carboxyglutamate protein (BGALP) which has been shown to inhibit adiposity and hepatic steatosis [84].

The liver, aside from being at the receiving end for NEFA, can transport lipids to peripheral tissues via VLDL. The assembly and secretion of VLDL is a complicated process that depends not only on substrate availability but also on co-translational regulation of ApoB and the microsomal triglyceride transfer protein (MTTP); reuptake of under-lipidated, immature particles; and the status of the intracellular secretory pathway [85]. Both *in vitro* and *in vivo* studies done on primary hepatocytes and dexamethasone-treated mice, respectively, showed increased VLDL triglycerides and plasma concentration of HDL particles [86–88]. Promotion of VLDL secretion by GCs is possibly due to increased production and stabilization of ApoB together with increased triglyceride synthesis [89]. Similarly, increased VLDL-TG production resulting in hypertriglyceridemia is observed in rats treated with dexamethasone for 2 weeks [90]. The rats also had impaired adipose tissue LPL activity which contributes to hypertriglyceridemia. In human cases of Cushing's syndrome, the rate of VLDL production, and consequently VLDL and LDL levels, is found to be elevated and peripheral clearance is unaffected [91]. Besides VLDL secretion, the receptor-mediated clearance of the remnants of triglyceride-rich lipoproteins (TRLs: chylomicrons, VLDL, IDL, and LDL) is also possibly regulated by GCs. It has been reported that the levels of these remnant particles are elevated in conditions of metabolic syndrome where hypertriglyceridemia and HPA hyperactivity are likewise observed [7, 92]. The major remnant receptors include the lipolysis-stimulated lipoprotein receptor (LSR), LDL receptor (LDLR), LDLR-related protein (LRP), and heparan sulfate proteoglycans (HSPGs) [7, 93]. With the exception of LDLR which has been shown to be down-regulated by GC treatment [94], no other studies have been done on how GC or the GR can affect receptor-mediated clearance of TRL remnant particles that can then impact on systemic triglyceride levels.

Effects of GCs on Cholesterol and Bile Acid Homeostasis

Cholesterol is an important lipid metabolite serving as a component of biomembranes and as precursor for the synthesis of steroids. Cholesterol transport in the body is largely dependent on LDL and HDL particles. Both interact with its respective receptors enabling endocytosis of the entire particle. Besides VLDL and TRL remnants, GCs are also shown to elevate HDL in the plasma of rats which can be attributed to the inhibition of hepatic lipase (HL) and activation of lecithin-cholesterol acyltransferase (LCAT) activity [95]. Similar results are reported in dexamethasone-treated livers of adrenalectomized rats [88], in overweight and obese individuals [96], and persons who received prednisone for 1 month as part of

rheumatic disease management [97]. Furthermore, GCs are shown to increase transcriptional activity of apolipoprotein A-I (ApoA1), the major protein component of HDL particles which is important for the transport of cholesterol from the peripheral tissues to the liver [98]. A dose-dependent effect of dexamethasone is also observed in the hepatocyte binding capacity of HDL in dexamethasone-treated adrenalectomized rats [99]. The HDL scavenger receptor (SCRAB1/SRB1) promotes glucocorticoid production by the adrenal gland [100] particularly in response to inflammation and bacterial endotoxins [101]. Furthermore, adrenal-specific SRB1 deficiency resulted into glucocorticoid insufficiency and lower VLDL and LDL levels suggesting potential cross-talk between the liver and adrenal glands [102]. In case of LDL, reports on the effects of GCs on its metabolism have been elusive. The negative effects of GCs on hepatic LDLR levels [94] enables one to speculate the pathophysiologic consequences of elevated GC levels but the limited, often contradicting, reports warrant further studies.

In the field of cholesterol handling by the liver, hepatocyte-specific GR loss-of-function reduced the serum hypercholesterolemia in obese mice [78]. This is also accompanied by higher hepatic expression of the sterol regulatory element binding protein 2 (SREBP2) and increased liver cholesterol levels suggesting functional role of the GR in hepatic cholesterol homeostasis. In another study, as well as Addison's patients, serum bile acids were elevated in the fasted state and systemic bile acid homeostasis was disrupted upon the fasted-fed transition [103]. This abnormality in bile acid homeostasis can be attributed to lower expression of the major basolateral hepatocyte bile acid transporter, Na^+-taurocholate transport protein (NTCP/SLC10A1) resulting in faulty trans-hepatic bile acid recycling [103]. The gene coding for NTCP is shown to be a direct GR target based on avidin-biotin DNA-binding (ABCD) and chromatin immunoprecipitation (ChIP) assays and studies in mice with mutant GR where DNA-binding and dimerization function was lost (GR^{dim}) [103, 104]. The impaired bile acid uptake likewise exacerbated development of gallstones in mice with hepatocyte-specific GR knockdown [103]. Furthermore, the mice did not gain as much weight as the control owing to reduced fat mass which could be due to lower feed efficiency brought by ineffective lipid digestion and absorption [103]. The findings though, are contradictory to what is observed in Cushing's patients who have elevated serum bile acid and in a separate study where liver-specific GR knockdown results in lower serum bile acid due to inhibition of FXR activity which then blunts bile acid synthesis [105]. Further studies are therefore required to clarify these discrepancies.

GC-Dependent Lipid Processes in Muscles and Macrophages

With the exception of macrophages and smooth muscles, little attention has been given to how glucocorticoids affect lipid metabolism in other tissues. In muscles, most studies have focused on the effects of GCs on protein metabolism. With regards

to lipids, dexamethasone has been shown to promote intramuscular fat accumulation in chicken by AMPK inhibition and mTOR activation [106]. The process is aggravated by saturated fats and alleviated by unsaturated fatty acids. This is contradictory to what has been reported in C2C12 myotubes where dexamethasone treatment resulted into dose-dependent reduction of expression of lipogenic genes (FASN, ACC, and GPAT) which can be reversed by the GR antagonist RU486 [107]. It has also been reported that GCs can induce excessive NEFA oxidation that can lead into muscle insulin resistance [108] and perturbation of equilibrium between fats and glucose as energy sources [109]. In rats, GC-induced insulin resistance has been shown to increase serum insulin and NEFA levels and decrease oxidative phosphorylation by producing ATP from phosphocreatine [110]. How GC/GR signaling exactly orchestrates these entire events in skeletal muscles, with the possibility of inter-organ cross-talk, remains to be studied. In smooth muscles, dexamethasone has been demonstrated to increase the rate of cholesteryl ester formation in cultured human smooth muscle cells [111] and *in vivo* [112] which has implications on the atherogenic effect of GCs. But whether the mechanism of GC-induced lipid oxidation in muscle is similar as in fats and the liver and how GCs promote cholesteryl ester accumulation in smooth muscles remain to be investigated. In macrophages, increased GC-dependent, esterification of cholesterol is likewise observed [112, 113], which provide a unifying theme by which GCs can adversely affect atherogenesis. Furthermore, it has been demonstrated also in macrophages that dexamethasone can decrease both mRNA and protein levels of the cholesterol transporter ATP-binding cassette transporter-A1 (ABCA1) and that apoA1-mediated cholesterol efflux is impeded [113] which would further support the hypothesis of GC-associated cardiovascular risk.

Concluding Remarks and Outlook

Apart from the peripheral functions of the GC/GR axis in metabolic control (Fig. 6.2), recent studies have established further ties between GC/GR signaling and regulatory functions of the central nervous system, osteoblasts as well as intestinal cells in energy homeostasis and lipid handling.

Together, these studies have substantially broadened the spectrum of GC target organs in energy homeostasis and revealed unexpected communication routes between peripheral and/or central organ compartments. GC/GR-dependent endocrine control beyond the classical GC-mediated pathways therefore represents a largely unexplored area of research that holds the promise for exciting discoveries in endocrine circuitry in the future. It can be anticipated that recent advances in –OMICS technologies and systems biology will provide substantial support for our further understanding of endocrine GC/GR signaling and its impact on metabolic health and disease.

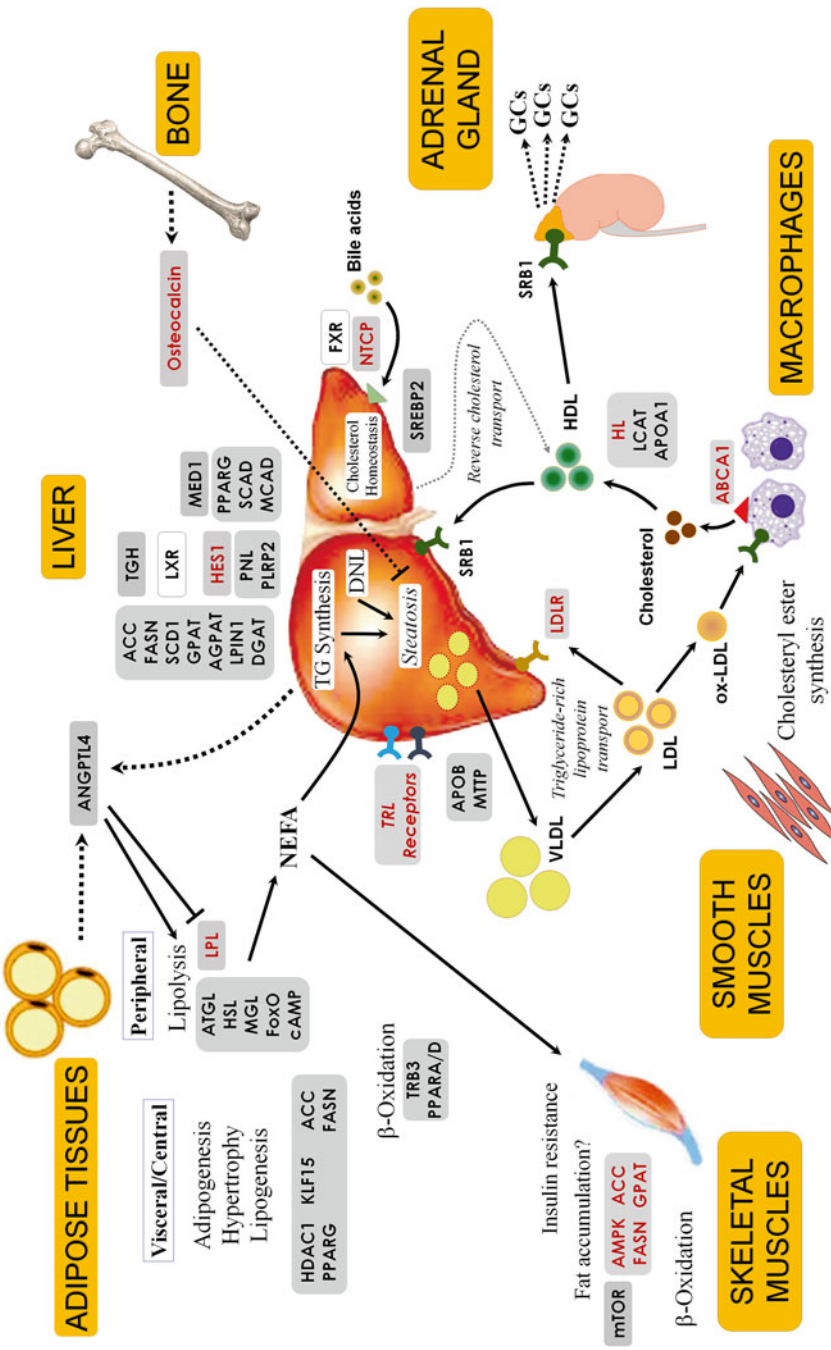

Fig. 6.2 GC/GR targets in lipid metabolism. Overview of lipid metabolic processes regulated by the GC/GR signaling in adipose tissues, the liver, bone, muscles, macrophages, and adrenal glands. Genes regulated by GCs in each metabolic process are listed in square-round boxes: genes in *black* texts are up-regulated; genes in *red* texts are inhibited by GCs

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