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Deconstructing the roles of glucocorticoids in adipose tissue biology and the development of central obesity

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Abstract

Central obesity is associated with insulin resistance and dyslipidemia. Thus, the mechanisms that control fat distribution and its impact on systemic metabolism have importance for understanding risk for diabetes and cardiovascular disease. Hypercortisolemia at the systemic (Cushing's syndrome) or local levels (due to adipose-specific overproduction via 11β-Hydroxysteroid dehydrogenase 1) results in the preferential expansion of central, especially visceral fat depots. At the same time, peripheral subcutaneous depots can become depleted. The biochemical and molecular mechanisms underlying the depot-specific actions of glucocorticoids (GCs) on adipose tissue function remain poorly understood. GCs exert pleiotropic effects on adipocyte metabolic, endocrine and immune function, and dampen adipose tissue inflammation. GCs also regulate multiple steps in the process of adipogenesis. Acting synergistically with insulin, GCs increase the expression of numerous genes involved in fat deposition. Variable effects of GC on lipolysis are reported, and GC can improve or impair insulin action depending on the experimental conditions. Thus, the net effect of GC on fat storage appears to depend on the physiologic context. The preferential effects of GC on visceral adipose tissue have been linked to higher cortisol production and glucocorticoid receptor expression, but the molecular details of the depot-dependent actions of GCs are only beginning to be understood. In addition, increasing evidence underlines the importance of circadian variations in GCs in relationship to the timing of meals for determining their anabolic actions on the adipocyte. In summary, although the molecular mechanisms remain to be fully elucidated, there is increasing evidence that GCs have multiple, depot-dependent effects on adipocyte gene expression and metabolism that promote central fat deposition.

1. Introduction

Adipose tissue stores excess energy as triglyceride (TG) and releases it as free fatty acids (FFA) depending on body needs. Adipose tissue is also an endocrine organ that secretes numerous peptide hormones and bioactive molecules that act in auto-, para- and endocrine fashions to regulate adipose tissue as well as systemic metabolism. The higher mass of dysfunctional adipose tissue in obesity may cause or exacerbate metabolic abnormalities that

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lead to type 2 diabetes, cardiovascular diseases, and several types of cancer. Adipose tissues or 'depots' are found in multiple locations throughout the body. Each has distinct developmental, structural, and functional features [64]. Visceral depots (omental and mesenteric) are found within the abdominal cavity associated with digestive organs, while subcutaneous (sc) depots are found under the skin. Fat accumulation in both visceral and abdominal sc depots confers increased risk for metabolic disease independent of total body fat, while fat accumulation in the lower body is protective [64,108]. Similarities between metabolic abnormalities in central obesity and glucocorticoid (GC) excess, i.e. Cushing's syndrome, have led to the hypothesis that derangements in GC metabolism and action in adipose tissue play pivotal roles in the development of obesity and pathogenesis of obesity related diseases. Indeed, visceral obesity has been appropriately described as "Cushing's disease of the omentum" [11].

The in vivo effects of GC are complex. Pathophysiological levels cause muscle protein breakdown as well as systemic insulin resistance, while physiological levels are crucial for mobilizing stored fuel for the "fight or flight response" as well as for replenishing fat stores when insulin levels rises with feeding. Most in vivo studies involve administration of high concentrations of GC that does not provide insight into how physiological variations in systemic and tissue cortisol levels throughout the day affect systemic and tissue-specific metabolism. Additionally, analysis of the in vivo consequences of hypercortisolemia on the adipocytes is partially confounded by alterations in food intake, compensatory hyperinsulinemia and activation of the sympathetic nervous system [66]. Studies of GC action in vitro are also often difficult to interpret as they usually involve continuous treatment with very high levels of dexamethasone (Dex), a type II glucocorticoid receptor (GR) agonist.

GCs have diverse effects on adipose tissue biology. They are required for induction of lipogenic genes, regulate lipolysis [85] and adipose endocrine function [9,29,60,63], and play an important role in restraining adipose tissue inflammation in obesity [84]. GCs are also required for the differentiation of adipocyte precursors [40,80] and the maintenance of adipogenic genes in cultured adipocytes and adipose tissue [63,126]. Increasing numbers of studies address the interactions of GC and insulin, and the impact of synergisms between these two major hormones in the regulation of fat distribution and function in vivo and in vitro.

Here we review available knowledge of the actions of GC on adipose tissue, attempting to distinguish GC effects on different cell types that reside within tissues, as well as studies using cell culture models that examine the direct effects of GC on the adipocyte. We will briefly review cellular and molecular mechanisms mediating GC action at prereceptor and receptor levels, and discuss current understanding of the mechanisms through which GCs affect adiposity and fat distribution.

2. Glucocorticoids promote fat deposition and central adiposity

The powerful effects of GC on adipose tissue accumulation are clearly demonstrated by early studies showing that adrenalectomy prevents obesity in Zucker rats and this is reversed by replacement of corticosterone [28]. In mouse models, overexpression of 11-beta hydroxysteroid dehydrogenase 1 (HSD1) using an adipose specific promoter (aP2) that produces high local concentration of corticosterone within adipose tissue results in the preferential expansion of mesenteric (visceral) fat due to adipocyte hypertrophy [72]. Conversely, genetic or pharmacological inactivation of HSD1 results in a lean, insulin-sensitive phenotype [51,53,75].

In humans, excess cortisol at the systemic level results in 2 to 5-fold increases in central, especially visceral adipose tissues (Cushing's syndrome), while peripheral sc depots waste [35,93,119]. Although the clinical literature describes peripheral fat wasting in Cushing's syndrome, the magnitudes of the effect at different sc sites using whole body imaging methods and its reversibility with treatment remain poorly documented. One study suggested that expected depot differences in adipocyte size between the two major sc depots, i.e. smaller abdominal than gluteo-femoral adipocytes, are lost in Cushing's syndrome [91], suggesting hypertrophy of abdominal adipocytes. The preferential expansion of abdominal sc adipose tissue in Cushing's syndrome is mediated, at least in part, by elevated activity of lipoprotein lipase (LPL), the rate-determining step for the hydrolysis and uptake of circulating TG-fatty acids into adipocytes, together with low lipolytic rates [91] (also as reviewed in [70]). Additional in vitro as well as in vivo studies using tracer methodologies are clearly needed to understand how acute and chronic hypercortisolemia promotes central fat deposition while wasting peripheral sc depots.

3. Do systemic or local excess glucocorticoids contribute to central adiposity?

3.1. Systemic cortisol levels are normal in obesity

Individuals under chronic, uncontrollable stress are more likely to have elevated levels of visceral fat [96]. Despite an increase in overall cortisol production and rates of turnover, circulating cortisol levels have been shown to be normal or low in obesity [65,105]. Subsequent studies revealed abnormalities in the hypothalamus-pituitary-adrenal (HPA) axis of the obese which are a function of body fat distribution rather than total fat mass. Repeated measurements of salivary cortisol in free-living subjects revealed an abnormal diurnal variation of cortisol which was positively associated with an upper body fat distribution as measured by waist-hip ratio (WHR) [96]. This abnormal pattern was characterized by low variability, absent circadian rhythm, low morning cortisol, and lack of meal-induced cortisol response [65,96,97], all of which have been associated with long-term over-activation (burn-out) of the HPA axis. Lower suppression of 8 A.M. cortisol after low dose Dex is reported among subjects with elevated WHR [65,82], but other studies show enhanced cortisol suppression after Dex among abdominally obese subjects [22]. Elevated response to corticotrophin releasing hormone (CRH) stimulation [83], and increased basal [66] and stimulated response to stress [24] in subjects with abdominal obesity, suggest over-activation of the HPA axis in these subjects. A recent study [46] showing active recycling of cortisol in metabolically active tissues highlights the difficulties of understanding interactions of central and peripheral mechanisms that modulate cortisol actions in vivo.

The consequences of the circadian variations in cortisol and interactions with meals for GC action within adipose tissue also deserve consideration. For example, a pulse of cortisol increases leptin only when given together with a meal or insulin [56,57]. Indeed GCs are important for regulating circadian phenomena at the whole body level. GCs connect the central hypothalamic clock with the peripheral clocks in multiple tissues, so that diurnal functions are in step with the environmental cycles of light and nutrition [4]. At the adipocyte level, supraphysiological doses of GC can acutely affect the expression and rhythmicity of clock genes [36,124]. Given that genetic disruption of clock genes specifically in adipose tissue causes obesity [81], future studies of how variations in the pattern of cortisol secretion affect regional adipose tissue deposition and function in humans are clearly needed. GC turnover rates in adipose tissue however, are low and possibly unaffected by acute fluctuations in circulating cortisol levels [47]. Thus, the local production of GC may be more important in the physiological context, as discussed below (section 3.2).

3.2. Local production of cortisol is increased in adipose tissue of obese subjects

While serum cortisol levels are not clearly increased in human obesity, increased local activation of cortisol from cortisone within adipose tissue is associated with obesity [23,50,62,88]. Intracellular cortisol levels are regulated by HSD1 and HSD2. HSD1, a NADPH dependent enzyme, is expressed in many tissues, including liver and adipose tissue, and acts predominantly as a reductase, generating cortisol in vivo. HSD2, expressed in kidney and colon, inactivates cortisol to cortisone, protecting the mineralocorticoid receptor (MR) from activation by cortisol.

HSD1 knockout mice are protected from high-fat diet induced obesity, hyperglycemia and dyslipidemia [51,53,75], while adipose overexpression of HSD1 results in obesity with metabolic syndrome [72]. HSD1 overexpression or knockout preferentially affects intraabdominal, especially mesenteric fat, in mouse [72,75]. Similarly, administration of an HSD1 inhibitor at a dose that does not affect food intake induces preferential loss of mesenteric fat in mice [7]. The HSD1 knockout mouse also exhibits depot- and diet-dependent effects on adipose inflammation and promotes sc fat distribution [120]. It will be important to understand how the fine tuning of intracellular cortisol production in specific adipose depots impacts inflammation and metabolism in obesity.

In humans, most but not all studies that examined the relationship of obesity to adipose HSD1 mRNA and reductase activity show positive correlations with BMI and adipocyte size [23,50,62,88,111]. It is not clear however, whether high adipose HSD1 expression is a cause or a compensatory mechanism in human obesity. It has been postulated that higher cortisol synthesis in visceral fat contributes to the preferential expansion of this depot. Consistent with this idea, one study found higher HSD1 reductase activity in stromal cell cultures derived from omental than abdominal sc adipose tissue [10]. Contradictory results showing no depot differences in HSD1 activity in fresh tissue are also reported [62,111] and thus, it is not clear whether increased local production of cortisol contributes significantly to visceral fat accumulation. Studies of human adipose tissue in organ culture showed that Dex causes a depot-specific feed-forward upregulation of HSD reductase activity in omental but not abdominal sc adipose tissue [62], suggesting a mechanism through which GC promote visceral obesity in response to stress.

HSD2 is reportedly expressed in non-adipocyte cell populations within human adipose tissues. While HSD2 expression level or its activity is not increased in obesity, several studies found that HSD2 expression levels are higher in omental than sc adipose tissue [62,116], suggesting higher cortisol turnover in the visceral depot. The higher rate of turnover may provide a mechanism to fine tune GC production and hence actions in this depot in response to nutrient or hormonal cues. Potential variations in local GC levels throughout the day and possible variations with meals have not yet been systemically studied. In this context, it is noteworthy that most studies of cortisol production and action in adipose tissue are conducted in the overnight fasted state. Basu et al [5] found that meal induced cortisol production and that was due to extrasplanchnic tissue production. Studies of tissue-specific meal-induced changes in the prereceptor metabolism of GC and their receptor-mediated actions will be important in understanding the complex physiology of this hormone in the context of obesity, overnutrition and the metabolic syndrome.

4. Molecular mechanisms governing glucocorticoid actions on adipocytes

4.1. Role of the type II glucocorticoid receptor

The action of GC on target cells is thought to be mediated by the type 2 glucocorticoid receptor (GR, NR3C1), a member of the nuclear receptor superfamily that is expressed in virtually all tissues. Unliganded GR resides in the cytoplasm as a heterocomplex with

several heat shock proteins and chaperone complexes [76]. Ligand binding triggers conformational changes in the receptor that result in dissociation from the heterocomplex and translocation into the nucleus. The GR homodimer binds to specific DNA locations, glucocorticoid response elements (GREs), and stimulates target gene expression. GR also associates with less well-defined negative GREs and transrepresses gene transcription. Once bound to the GREs, conformational changes in the receptor lead to chromatin remodeling and recruitment of cofactors and the transcriptional machinery.

GR is known to interact with other transcription factors through direct protein-protein interactions, mutually regulating each other's transcriptional activities. GR interaction with AP-1 and NF-κB is important for the GC-mediated transrepression of inflammatory cytokines [8] and its interaction with COUP-TFII is important for GC actions on metabolic gene expression [18]. GR is also known to associate with STAT3 [59], STAT5 [6] and estrogen receptor [17]. In addition, cytoplasmic or membrane bound GR causes rapid, nongenomic signaling [103], adding to the complexity of GC-GR mediated actions.

Recent advances in the GR biology demonstrate that multiple transcriptional (α and β) and translational isoforms (A, B, C1, 2, 3, and D1, 2, 3) are expressed in cell type or tissue specific manners [76]. The GRα and β are generated through alternative splicing of exon 9 (9α and 9β). Similar to GRα, GRβ is ubiquitously expressed, but overall at lower levels than GRα. GRβ acts as dominant negative inhibitor of GRα and its expression is increased by proinflammatory cytokines, leading to GC resistance [122]. GRβ also exhibits GRα-independent transcriptional activity [52]. Additional splice variants, GRγ, GR-A, and GR-P are reported and impact on GC signaling [76]. Cidlowski's group demonstrated that eight GR protein subtypes are generated from GRα mRNA by alternative translation initiation [67]. Use of different translation initiation sites is tissue specific and thus, relative abundance of each isoforms differs between tissues. GR isoforms activate both unique and common genes [67], revealing complexity of GC signaling through GR translational isoforms. We have detected these translational isoforms in human adipose tissues (unpublished observation, MJL and SKF). Their roles in modulating GC action in adipocytes and other cells within adipose tissue remain to be elucidated.

GR transcriptional activity is further modulated by post-translational modifications. Human GR is phosphorylated on its N-terminus at three major sites (serine 203, 211 and 226) [48]. The phosphorylation of GR affects the transcriptional activities of GR by altering ligand- and DNA-binding affinity and cofactor recruitment. Phosphorylation at serine 211 is ligand dependent and associated with nuclear localization and activation. Serine 226 is targeted by mitogen activated kinases (MAPKs), and this mechanism links high levels of inflammatory cytokines to GC resistance in a number of disease states [48,107]. It is logical to postulate that the high inflammatory cytokine levels in obese vs. lean adipose tissues may increase the expression levels of GRβ as well as phosphorylation at serine 226 and lead to GC resistance, but no studies to our knowledge have addressed this issue.

4.2. Role of the type I glucocorticoid receptor in adipose biology

Recent studies demonstrate that the mineralocorticoid receptor (MR, NR3C2), a type 1 glucocorticoid receptor, is also expressed in adipose tissue [44] and play important roles in adipogenesis and adipose endocrine function [45,71]. The relative contribution of GC-GR and GC-MR in a specific tissue is far less than clear and depends on the relative abundance of MR and GR, circulating levels of GC and aldosterone, and local conversion of cortisone-cortisol by HSD1 and HSD2. MR binds to cortisol with 10-fold higher affinity than GR [3] and in classical MR target tissues such as kidney, MR activation by cortisol is spared by inactivation of cortisol via HSD2. Because circulating levels of aldosterone are 100–1000 times lower than cortisone and HSD2 is expressed at much lower levels than HSD1 in

adipose tissue [23,62,116], it is conceivable that high local concentration of cortisol within adipose tissue may activate both GR and MR.

MR activation increases while GR activation decreases proinflammatory adipokine expression such as interleukin-6 (IL-6) and plasminogen activator inhibitor 1 [45]. The selective MR antagonist eplerenone reduces adipose expression of proinflammatory genes and infiltration of macrophages into adipose tissue with improvement in insulin sensitivity in obese rodent models [38,43,44]. In contrast, Dex (a selective agonist for GR) decreases proinflammatory cytokine expression in adipose tissue [9,29,63] and macrophage infiltration into adipose tissue in vivo [84]. Both HSD1 and MR expression levels are increased in adipose tissue of obesity, while HSD2 and GR are not [44,62,116]. Thus, the relative contribution of GC-MR pathway may be increased in obesity and contribute to adipose tissue inflammation in obesity.

4.3. Depot dependent actions of glucocorticoids: role of GR and MR

Intraabdominal fat is thought to be more responsive to GCs than is sc adipose tissue, explaining the preferential accumulation of fat in this depot with chronic GC excess. Accordingly, studies found that GC binding to tissue homogenates and GR mRNA expression levels are 2 to 4-fold greater in omental than sc adipose tissue [73,86,90,116]. However, recent developments in our knowledge of GR biology reveal the more complex nature of GC signaling in adipose tissue. Thus, the relative abundance of GRα may not completely explain the depot-differences in GC actions. Rather, levels of transcriptional and translational GR isoforms, the phosphorylation status of GR, and expression levels of MR and GR-interacting partners, are likely to contribute to the depot-dependent effects of GCs. Inflammatory cytokines including TNF increase GRβ expression [122] and phosphorylation of GRα at serine 226 and decrease its transcriptional activity [64]. The higher inflammatory environment in visceral vs. sc may well play a role in depot differences in GC action. Further, mRNA expression levels of MR are also higher in omental than sc depot ([44] and our unpublished observation, MJL and SKF). Thus, we postulate that the relative contribution of the MR compared to the GR pathway may be amplified in human visceral adipose tissues.

5. Glucocorticoid actions on adipose tissue function

GCs affect almost every aspect of adipose tissue, including development, metabolism, and endocrine function (Figure 1).

5.1. Glucocorticoids and adipogenesis

GCs are required for full differentiation of adipocytes. GC actions on adipogenesis are explained by their anti-proliferative effects on preadipocytes [15,40], induction of a key adipogenic transcription factor, C/EBPbeta, as well as suppression of Pref-1 and Runx2 [110,123,127]. Several differences are noted for the mechanisms through which GCs enhance adipogenesis between the two most commonly used preadipocyte models, 3T3-L1 and primary human preadipocytes. GCs are required for cell survival during the clonal expansion that precedes terminal differentiation in 3T3-L1 but not in human preadipocytes [110]. GCs sensitize insulin signaling in human preadipocytes and this ‘priming’ action enhances their responses to adipogenic stimuli [109]. In contrast, this does not occur in 3T3-L1 cells [109], which are less committed to an adipocyte cell fate compared to human preadipocytes. Whether visceral and sc preadipocytes are differentially sensitive to this ‘priming’ action of GC to induce adipogenesis is unknown.

While the proadipogenic effects of GCs are well accepted, whether their effects are MR or GR is not clear. Recent studies demonstrate that MR rather than GR is important for the

proadipogenic effects of GCs in 3T3-L1 and mouse and human preadipocytes [13,14,45]. In primary human preadipocytes however, we found contradictory results. MR is expressed at much lower levels than GR, and RNAi-mediated suppression of GR but not MR blocked GC-stimulation of adipogenesis in primary human preadipocytes (unpublished observation, MJL and SKF). Adipose-specific GR or MR knockout mouse models will be able to determine whether MR or GR mediates GC actions on adipogenesis in vivo.

Depot-dependent actions of GC on adipogenesis have been implicated in rodent models. Corticosterone administration to rats increases intraabdominal depots (mesenteric and epididymal) but not sc ones [12,92]. The appearance of smaller and more numerous adipocytes in the mesenteric fat after corticosterone administration [12] suggest that increases in adipose tissue mass occurred through preadipocyte differentiation rather than adipocyte hypertrophy. Data on humans are scarce. Whether the preferential increase in visceral depot that is observed in subjects with Cushing's syndrome [35,119] is due to increase in adipogenesis or hypertrophy of existing adipocytes or both is not known. In addition, whether GCs differentially affect differentiation of preadipocytes derived from visceral vs. abdominal and limb sc adipose tissues is also not established. Omental preadipocytes from females but not males contain lower levels of GR mRNA and GC binding, potentially contributing to depot, sex-dependent differences in preadipocyte differentiation [49].

5.2. Glucocorticoid regulation of adipose gene networks

GCs are known to affect up to 20% of adipose expressed genes in microarray studies [63,126]. GCs induce genes in metabolic pathways (expressed mainly in adipocytes) while suppressing genes in immune/inflammatory and proapoptotic pathways. As microarray studies cannot identify whether GC affected genes are primary or secondary targets of GR, ChIP-seq technologies have been applied [126]. More than 8840 genome locations are identified as GR binding regions (GBR) upon Dex treatment in 3T3-L1 adipocytes. When ChIP-seq data are compared with transcriptome analysis, 54% of genes that are regulated by 6-h Dex treatment contain or are located nearby GBRs. There is little overlap between the GR targets identified with ChIP-seq between different cell types [87], underlining the cell type specific effects of the GC-GR pathway. The specificity of GC actions may be determined by expression levels of GR isoforms and the phosphorylation state of GR, but no studies to date have addressed this possibility.

5.3. Glucocorticoids and adipose tissue metabolism

Adipose tissues store excess energy as neutral lipids, TG, and release it as FFA and glycerol in highly regulated fashion. TG is synthesized from FFA esterified to a glyceride-glycerol backbone. The glyceride-glycerol backbone is derived from glucose and the majority of FFA is delivered through lipoprotein lipase (LPL) breakdown of circulating TG in chylomicron or very low density lipoprotein (VLDL), as de novo lipogenesis (DNL) is minimal in normal situation [42]. GCs are known to affect almost every aspect of these adipose metabolic processes (Figure 2A). The effects of GC on adipocyte glucose metabolism [1] and lipid metabolism [85] have been previously reviewed so we only briefly discuss them here.

5.3.1. Glucocorticoid effects on adipocyte glucose metabolism—GC treatment in vitro, in the absence of insulin, have been shown to decrease glucose uptake and metabolism (oxidation into CO_2 and to glyceride-glycerol and FA synthesis) [27,31,37,77] with a time lag of 1–2 hours. In addition, pretreatment with GC antagonizes the ability of insulin to stimulate glucose uptake in adipocytes through different mechanisms depending on the exposure time. Acutely, GCs do not affect insulin binding, thus short-term effects of GC might be explained by glucose transporter translocation [31,77]. Chronic Dex-impairment of

insulin-stimulated glucose uptake is explained through decreases in insulin binding, expression of insulin receptor and insulin receptor substrate 1 (IRS1), and translocation of glucose transporter (GLUT4) [31,37,77,98,113]. Dex effects on basal glucose uptake however, are more pronounced than its antagonism of the insulin-stimulated glucose uptake. Thus, Dex actually increases fold over stimulation at maximal insulin concentrations [31]. Similarly, enhanced insulin signaling and glucose uptake following pretreatment with GC in human adipocytes [32,34] and preadipocytes [109] have been reported.

GCs also exert depot-dependent effects on insulin signaling, glucose uptake and the expression of insulin signaling proteins [41,69]. GCs increase IRS2 expression and insulin stimulation of AKT phosphorylation in abdominal sc but not omental adipocytes [41], while chronically GCs down-regulate components of the insulin signaling in omental but not abdominal sc adipose tissue [69].

5.3.2. Glucocorticoids and lipid storage, additive or synergistic effects with insulin to increase lipid synthesis—GCs differentially affect lipid storage depending on nutritional or hormonal conditions. While GCs decrease lipogenesis and FFA uptake in basal or fasting conditions [33,118], GCs act additively or synergistically with insulin to upregulate lipogenesis [33,74,121]. GC induction of DNL is explained by stimulation of key enzymes, acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) [63,121] (Figure 2A). DNL in adipose tissue is a minor contributor to total TG-FA [42] in humans eating moderate fat diets and the majority of FFA is derived from LPL breakdown of circulating TG-rich lipoproteins. GCs induce adipose LPL mRNA expression and activity and enzymes of TG synthesis with greater effects in omental than abdominal sc [2,30,63,79], and this mechanism may contribute to the hypertrophy of omental adipocytes with excess GC. The sensitivity and responsiveness of different sc depots, i.e. abdominal vs. gluteo-femoral, to GCs have not been studied, but may contribute to variations in fat distribution.

5.3.3. Glucocorticoids and lipolysis—GCs are widely cited as being lipolytic. However, results differ depending on the concentration and duration of treatment and the experimental model systems used. Although infusion of fairly high concentrations of GC increases systemic FFA and glycerol within several hours in overnight fasted humans [19–21,41,99,100], cortisol infusion actually decreases abdominal sc adipose tissue lipolysis as measured by the arterio-venous difference across this depot [99]. The authors suggested that depot-specific effect of cortisol on the enzymes of intracellular lipolysis (hormone-sensitive lipase, HSL) and intravascular lipolysis (LPL) may explain how cortisol could acutely increase systemic lipolysis (glycerol and FA rate of appearance) while chronically higher levels would promote net central fat deposition over the long-term. A recent study demonstrated that systemic hydrocortisone infusion increases lipolysis, but the magnitude of suppression by insulin is actually increased [41].

Analysis of data from long-term (days to weeks) infusion of GC [12,114,125,126] is complicated by compensatory hyperinsulinemia which may chronically promote higher FA flux via induction of insulin resistance and activation of the sympathetic nervous system. In addition, GC-stimulation of beta adrenergic receptors and responsiveness to beta-adrenergic agonists [55,58,68,94] also contribute to high lipolysis after chronic GC treatment.

Results from in vitro studies testing the effects of GC on lipolysis using adipocytes and adipose tissue in culture are conflicting. In 3T3-L1 adipocytes and rat adipocytes, GCs increase lipolysis [12,125]. Adipocytes isolated after in vivo GC treatment also exhibit higher rates of lipolysis in vitro [12,54]. The stimulatory effects of GC on lipolysis have been attributed to its induction of adipose triglyceride lipase (ATGL) and HSL, and down-regulation of phosphodiesterase 3B (PDE3B) [12,54,125]. In contrast, we did not find any

significant effects of GC (Dex) on lipolysis in primary cultures of newly-differentiated human adipocytes [61]. In human adipose tissue explants, GC does not affect [26], inhibit [78], or antagonize insulin-stimulated lipolysis ([16] and our unpublished observation, MJL and SKF).

GCs have permissive effects on growth hormone (GH) and catecholamines to increase lipolysis. The permissive effects of GC on GH action are demonstrated in vivo [21], in rat adipocytes [27], and in human adipose tissue [26,78]. GCs are also required for normal response to catecholamine or fasting induction of lipolysis [25]. Similarly, in primary human adipocytes, we found that Dex enhances responses to beta-adrenergic stimulation [61].

Several studies showed that chronic exposure of human adipose tissue and 3T3-L1 adipocytes or mice in vivo to GCs increases genes involved in lipid storage and mobilization simultaneously [26,63,126]. Recently, Hellerstein's group demonstrated that increased cycling between TG and FFAs in adipose tissues of Cushingoid CRH-Tg mice in vivo [39]. Thus, it appears that GCs, at least in long-term, increase lipid turnover in adipose tissue (Figure 2B). Factors that tip the balance toward TG synthesis over breakdown may promote the hypertrophy of existing adipocytes in a depot-dependent manner and hence affect regional adiposity.

5.4. Glucocorticoid modulation of adipose endocrine function

Adipose tissue secretes numerous peptide hormones and cytokines. The adipocytes themselves produce many of these, including leptin, adiponectin, retinol binding protein 4 (RBP4), and serum amyloid A (SAA), while most proinflammatory cytokines and chemokines are produced by non-adipose cells within the adipose tissue [112]. GCs regulate the production of many of these adipokines. GCs increase leptin expression [60], while thier effects on adiponectin are still controversial [106]. As expected from their well known anti-inflammatory actions, GCs decrease inflammatory cytokines, namely IL-6, IL-8, and TNF in intact samples of adipose tissue [9,29]. Accordingly, the most significantly suppressed pathway after Dex treatment in human adipose tissue is immune/inflammatory responses [63]. Dex however, induces some immune/inflammatory genes that are known to be involved in acute phase response or innate immunity (SAA, Complement factor 7, 1q, and D, RBP4, and metallothioneins). Many of these Dex-induced immune genes are expressed in mature adipocytes, while suppressed genes are mainly expressed in stromal cells [112], demonstrating cell type specific effects of Dex within adipose tissue.

6. Glucocorticoids and brown adipose tissue

Metabolically active brown adipose tissue is believed to be present in adult humans and may play role in energy homeostasis and weight control [89]. While GCs promote brown preadipocyte differentiation [101], they inhibit uncoupling protein 1 (UCP1) expression and activity in brown adipocytes [102,117]. Accordingly, corticosterone administration to rats decreases thermogenic activity and UCP1 expression while increasing lipid accumulation in BAT [104]. These data demonstrate that GCs impair brown adipose tissue function and promote a 'brown' to 'white' phenotypic conversion.

7. Glucocorticoid regulated pathways as therapeutic targets

GCs are widely prescribed due to their anti-inflammatory or immunosuppressive effects. Chronic GCs, however, result in weight gain, hypertension and increased risk for diabetes. GC-transactivated genes are implicated in the pathogenesis of such side effects, while GR interactions with AP-1 and NF-κB are important in its anti-inflammatory actions. Thus, selective GR modulators that favor transrepression over transactivation are in development

[115]. In addition, clinical trials testing the effectiveness of HSD1 inhibitors for the treatment for obesity and metabolic diseases are under the investigation [95].

8. Conclusion

GCs have profound effects on adipose tissue, adipogenesis and adipose tissue metabolic and endocrine function. With chronic excess GC, produced systemically or through local adipose tissue conversion, fat accumulates in central adipose depots and contributes to metabolic derangements. The mechanisms through which high GCs promote the preferential expansion of visceral adipose depots remain incompletely understood. Intraabdominal depots are thought to be more responsive to GC due to high GR expression, leading to expansion of this depot. In addition, the type 1 glucocorticoid receptor, MR is expressed in adipose tissue, and mediates several actions of GC. The molecular complexity in GR biology in adipocytes, specifically the roles of multiple GR isoforms, interactions of GR with other transcription factors in adipocytes are emerging. Understanding the cross-talk of GR and inflammatory pathways via post-translational modifications of GR, is beginning to be understood and hold promise for the development of novel therapies for abdominal obesity and its deleterious metabolic consequences.

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Highlights

- Glucocorticoids (GC) regulate how much fat is stored in specific fat depots.
- Gucocorticoids regulate adipogenesis, and adipose metabolic and endocrine function.
- Central fat depots are more responsive glucocorticoids.
- The prereceptor activation of cortisone to cortisol regulates local fat distribution.
- Type I and II glucocorticoid receptors are both important in adipocytes.

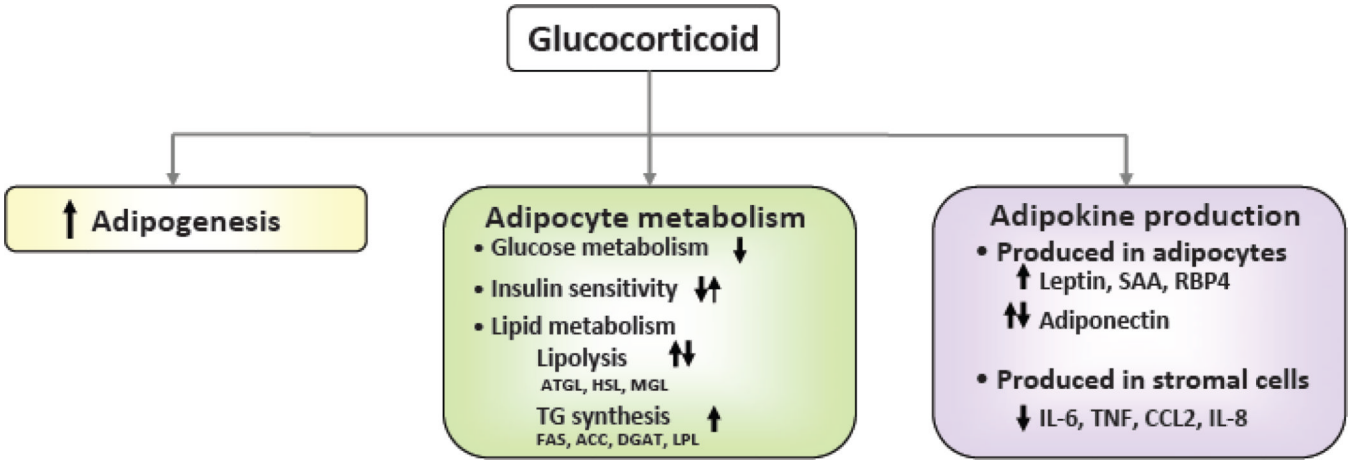

Figure 1. Pleiotropic actions of glucocorticoids in adipose tissue

GCs influence multiple aspects of adipose tissue biology: adipogenesis, metabolism, inflammation and adipokine production. Arrows indicates the direction of reported changes in experiments conducted under different conditions. Specifying these conditions, as discussed in the text, is essential for developing a full understanding of GC action.

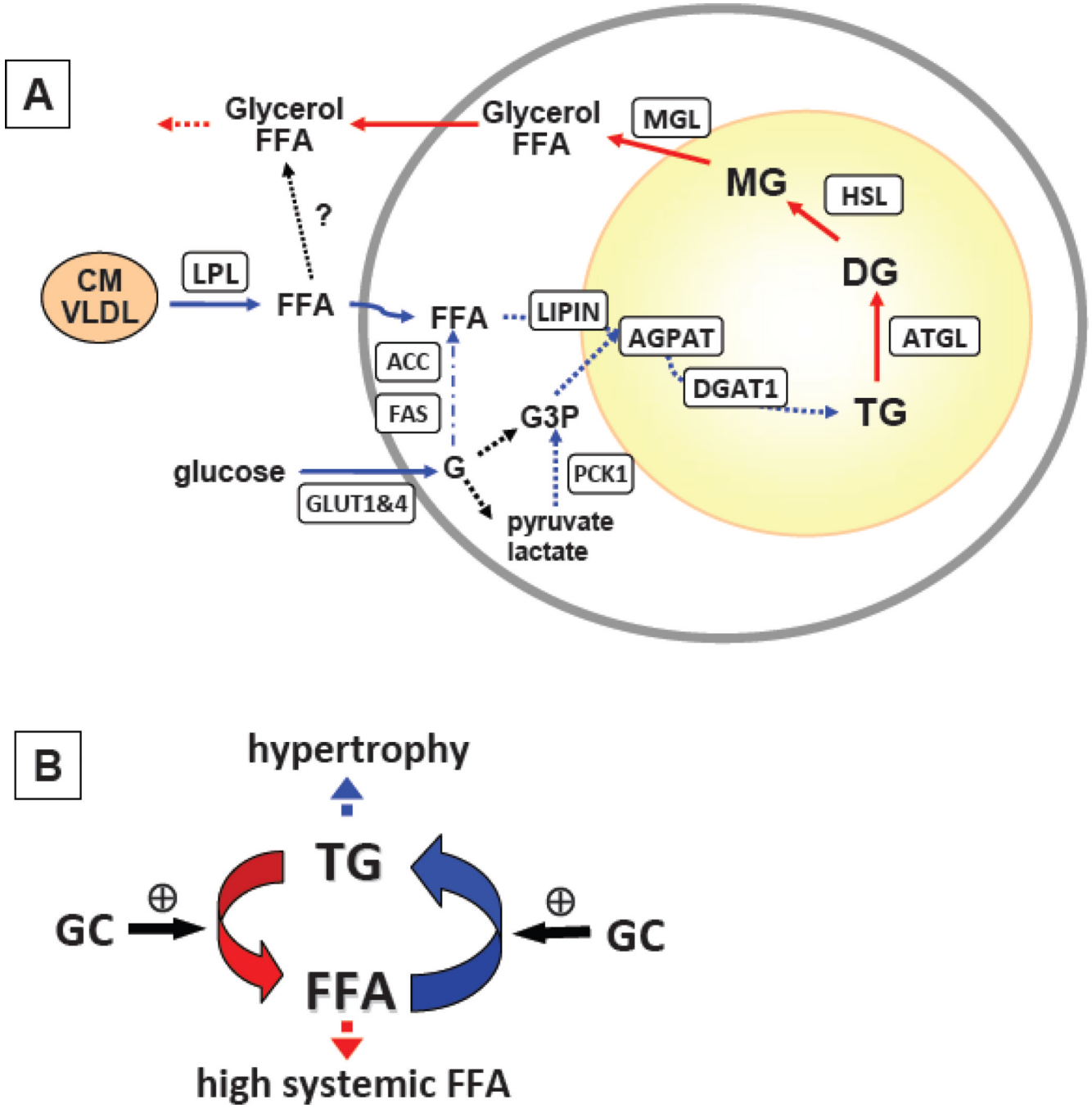

Figure 2. Glucocorticoids simultaneously increase pathways of TG synthesis and breakdown

A. GCs especially when added in the presence of insulin, mimicking the fed state, induce the expression of genes involved in lipid uptake (LPL), TG synthesis (LIPIN, AGPAT, DGAT1) and de novo lipogenesis (ACC, FAS). GCs also increase the expression of genes involved in TG hydrolysis (ATGL, HSL, MGL). GC induction of PCK1 expression is likely to play a role in glyceroneogenesis, contributing to TG synthetic pathway. **B**. GCs increase lipid turnover in adipose tissue. While GCs are widely cited as lipolytic and thought to increase systemic FFA, they also increase lipid uptake and TG synthesis. Factors that tip this balance

toward TG synthesis in a depot-dependent manner may lead to hypertrophy of existing adipocytes and hence affect regional adiposity.