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Mechanisms of Glucocorticoid-Induced Insulin Resistance:

Focus on Adipose Tissue Function and Lipid Metabolism

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INTRODUCTION

Chronic glucocorticoid (GC) exposure in humans is well known to result in whole-body insulin resistance and obesity. Cushing syndrome, an endocrine disorder characterized by chronic endogenous or exogenous GC overexposure, increases visceral and trunk subcutaneous adipose tissue and causes insulin resistance.[1,2] Likewise, abdominal obesity associated with the metabolic syndrome is linked with insulin resistance, cardiovascular risk, and decreased survival. Although endogenous Cushing syndrome is rare, the current prevalence of oral GC use in as high as 2.5% of the population makes insulin resistance and obesity resulting from exogenous GC exposure an important public health problem.[3] Moreover, subtle forms of endogenous GC excess are seen in the setting of chronic stress owing to activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased production of adrenal cortisol. Furthermore, so-called common obesity is believed to be associated with abnormalities in the HPA axis including the presence of increased local production of GCs in the adipose tissue, alterations in cortisol circadian rhythm, and enhanced susceptibility of the HPA axis to be activated, all of which result in greater GC exposure over time. Thus, the study of GC-induced obesity and its adverse metabolic profile has become increasingly important.

Adipose tissue is a complex endocrine and immune organ, responding to and, in turn, releasing signals that represent or reflect metabolic and cardiovascular risk factors.[4] In fact, a consensus statement published by the American Diabetes Association and the American Heart Association stated that “obesity is a visible marker of other underlying risk factors that can be addressed.”[5] These underlying risks include the metabolic syndrome (abdominal obesity, hypertension, elevated triglycerides, decreased high-density lipoprotein [HDL], and insulin resistance/impaired fasting glucose) as well as a low-grade proinflammatory state[6] that confers an increased risk for atherosclerosis and cardiovascular events.[7,8] Individuals with hypercortisolism have a 4-fold higher mortality rate than the general population because of cardiovascular complications, likely related to the associated obesity and insulin resistance.[9] This article reviews the mechanisms by which supraphysiologic GC exposure promotes insulin resistance, focusing in particular on the effects on adipose tissue function and lipid metabolism.

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MECHANISMS OF GC-INDUCED INSULIN RESISTANCE

Insulin resistance, the common thread between obesity, the metabolic syndrome, and type 2 diabetes mellitus, is defined as the impaired ability of insulin to control nutrient partitioning in target organs. In adipose tissue, insulin fails to restrain lipolysis and increase glucose uptake; in liver, to inhibit hepatic gluconeogenesis and glycogenolysis; and in muscle, to induce glucose uptake. A critical function of GCs is to liberate energy substrates (ie, glucose, amino acids, and fatty acids [FA]), and thus ensure their availability for mitochondrial oxidation in fight-or-flight conditions. Thus, GCs enhance muscle protein breakdown, adipose tissue lipolysis, and hepatic gluconeogenesis, and reduce glucose utilization, effects which elevate circulating glucose concentrations (summarized in Fig. 1). Chronic GC overexposure alters body composition, which includes expansion of trunk adipose tissue depots, and impairs metabolism and insulin action, resulting in hyperglycemia and dyslipidemia.

TISSUE-SPECIFIC REGULATION OF INSULIN RESISTANCE

GC Regulation of Adipose Tissue Functionality, Mass, and Distribution

GC regulation of white adipose tissue lipolysis—Adipose tissue function is a key determinant of whole-body glucose and lipid homeostasis. The role of GCs in regulating adipose tissue function is complex and context dependent. GCs induce preadipocyte differentiation,[10] but also adipose tissue lipolysis[11–14] in some settings. Specifically, some,[11,12] but not all[15] in vitro data show that when dexamethasone is added to rat adipocyte cultures, glycerol (a product of lipolysis) increases, in the context of increased mRNA expression of the 2 key lipolytic enzymes hormone-sensitive lipase (HSL)[12] and adipose triglyceride lipase.[16] Of note, one study showed that cortisol removal further increased 3T3-L1 lipolytic rates, suggesting that GC deficiency can increase basal lipolysis,[11] an unstudied potential mechanism that could underpin the cachexia of adrenal insufficiency. Physiologic doses of GCs maintain many biological functions such as vascular tone, and lipolysis may be another such function. Thus, the permissive effects of physiologic doses of GCs in maintaining normal lipolysis should not be confused with the effects of hyper-cortisolemia. Indeed, a single dose of high GCs induces lipolysis in vivo in rats and humans, although it remains unclear as to whether chronic GC exposure does the same.[11,13,14] Increased lipolysis will result in elevated circulating free FA (unless FA utilization is increased), and elevated circulating FA in turn can induce insulin resistance.[12,17] Thus, the diabetogenic effects of GCs are likely due to not only enhanced hepatic gluconeogenesis and impaired glucose uptake in muscle but also increased circulating free FA levels originating from increased adipose tissue lipolysis.

The role of GCs in the regulation of lipolysis also varies based on species, the specific adipose tissue depot,[18] and concentration and chronicity of GC exposure. For instance, chronic GCs increase circulating insulin, a potent antilipolytic hormone, but also decrease its action in some tissues. On the other hand, chronic GC exposure is associated with adipose tissue expansion, suggesting an increase in total body lipogenesis and, despite a possible increase in lipolysis, a positive balance of lipid storage in adipose tissue. To date, only 2 small studies have investigated lipolysis in chronic endogenous GC exposure caused by Cushing syndrome, and the results point to distinct differences between direct effects of GCs on adipose tissue and in vivo effects. Specifically, glycerol release was reduced in adipose tissue from individuals with active Cushing syndrome when assessed ex vivo from a biopsy,[19] consistent with decreased lipolysis in active Cushing syndrome.[19] However, in vivo adipose tissue glycerol release as studied through microdialysis[20] was increased, signifying augmented lipolysis. Thus it is likely that GCs regulate factors such as hormones, cytokines, or neuronal signals in tissues other than adipose, which indirectly control adipose

tissue functionality and may override the direct effects of GCs on adipose tissue. Further clinical investigation is needed to dissect these factors.

GC regulation of de novo lipogenesis in white adipose tissue—Our understanding of the role of de novo lipogenesis in adipose tissue and its role in whole-body energy homeostasis is still evolving. Although adipose tissue expansion caused by chronic GCs suggests an increase in total body lipogenesis, recent data suggest that de novo lipogenesis in adipose tissue is a marker of metabolic health and may be reduced in human obesity.[21–24] In the human adipocyte (Chub-S7) cell line, but also in primary cultures of human subcutaneous and omental adipocytes, cortisol and cortisone treatment decreased lipogenesis, demonstrated by decreased ^{14}C-acetate incorporation into lipid, in the context of reductions in acetyl coenzyme A carboxylase (ACC) mRNA expression and increases in the inactivating phosphorylation of the ACC protein.[25] Furthermore, inhibition of 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1), which prevents conversion of inactive cortisone to active cortisol, prevented cortisone-mediated suppression of lipogenesis. In this study, low-dose dexamethasone pretreatment of Chub-S7 cells enhanced the ability of insulin to stimulate de novo lipogenesis, suggesting that insulin concentrations are critical for GC regulation of lipogenesis.[25] Whether enhanced total body lipogenesis that occurs in humans in response to chronic GC exposure reflects adipose tissue or hepatic lipogenesis is not known but, based on the higher contribution of hepatic lipogenesis to whole-body lipogenesis,[26] one would expect GC-induced lipogenesis to be primarily hepatic in origin.

GC regulation of insulin sensitivity in white adipose tissue—Although GCs result in whole-body insulin resistance, this does not necessarily mean that they impair insulin action in each tissue. Recent work has shown that both endogenous and synthetic GCs may in fact enhance insulin signaling and action in human adipose tissue.[25,27–29] For example, short-term (24 hours) pretreatment with GCs enhanced insulin-stimulated tyrosine phosphorylation of insulin receptor (IR) substrate protein 1 (IRS1) and protein kinase B/akt phosphorylation in human adipocytes derived from a subcutaneous adipose tissue biopsy.[27] These effects, which were dose dependent and time dependent, occurred in the context of increased expression of IR, IRS2, and the p85 regulatory subunit of phopshoinositide-3-kinase.[27,28] Subsequent work showed that both short-term (24 hours) and long-term (7 days) exposure of immortalized differentiated human adipocytes (Chub-S7 cells) to dexamethasone,[29] enhanced insulin signaling, and seemed to prevent the insulin resistance caused by chronic high-dose insulin treatment.[29] This finding is in agreement with a recent in vivo study performed in humans, whereby overnight administration of hydrocortisone resulted in systemic insulin resistance, but enhanced insulin action in subcutaneous adipose tissue.[30]

These findings suggest that GCs may regulate insulin action in a tissue-dependent manner, sensitizing subcutaneous adipose tissue to insulin but doing the opposite in muscle, although this has not been confirmed by all studies.[31–33] This GC-mediated enhancement of adipose tissue insulin sensitivity could in turn drive its expansion, leading to obesity, because insulin and GCs are critical factors in adipocyte differentiation and lipid accumulation. Thus, although it seems somewhat paradoxic, increased adiposity caused by excessive GC exposure may in fact be due to enhanced insulin sensitivity of adipose tissue. This process can be understood as a compensatory adaptation whereby, by favoring storage of lipids in adipose tissue, GCs ameliorate the lipotoxicity that would otherwise arise from the increased caloric intake and whole-body lipogenesis observed in Cushing syndrome. However, these findings need to be explored in vivo in animal and human studies in the setting of chronic GC exposure where obesity, global insulin resistance, and hyperinsulinemia may eventually exhaust the ability of adipose tissue to expand and function properly, which in turn may impair insulin action in adipose tissue.

Finally, the biology of adipose tissue has important depot-specific differences, and it is not known to what extent the GC effects are depot dependent. The aforementioned findings elucidate the expansion of subcutaneous but not visceral adipose tissue. For example, one study showed that in omental but not subcutaneous cells, GCs decreased insulin-stimulated glucose uptake,[32] but whether this was due to decreased insulin signaling remains to be determined. Thus, the effects of GCs on insulin sensitivity may differ between visceral and subcutaneous adipose tissue.

Chronic in vivo GC effects on adipogenesis and white adipose tissue mass and distribution in humans: studies on Cushing syndrome—By numerous potential mechanisms, including the production of proinflammatory cytokines and increased portal FA delivery to the liver,[34] abdominal obesity, the accumulation of visceral and trunk subcutaneous fat, is closely linked to the development of insulin resistance, dyslipidemia, and cardiovascular risk.[35–40] Of importance are not only the absolute increases in abdominal fat mass but also the proportion of adipose to muscle mass. For example, an elevated ratio of both visceral to total fat and visceral fat to thigh muscle have been linked to insulin resistance, hepatic steatosis, and the metabolic syndrome.[41]

Chronic excessive GC exposure also increases the ratio of visceral fat to both total fat and muscle. These effects of GCs manifest most clearly in patients with Cushing syndrome, in whom profound increases in total and visceral adipose tissue mass is commonly observed[1,19,42–49] while increases in the subcutaneous depots are moderate.[1] Specifically, although the mass of the total subcutaneous adipose tissue is not different between patients and controls, trunk subcutaneous adipose tissue is enlarged, which, similarly to visceral adipose tissue, is associated with adverse metabolic sequelae.[1] Although some studies have reported lower limb subcutaneous adipose tissue mass in Cushing patients,[46] when quantified by whole-body magnetic resonance imaging (MRI) (the gold standard for assessment of body composition), limb subcutaneous adipose tissue in Cushing patients was not different in comparison with controls.[1]

Normalization of cortisol concentrations in patients with Cushing disease significantly reduces the mass of the total, trunk, subcutaneous, and visceral adipose tissue.[2] Furthermore, cortisol normalization alters adipose tissue distribution, resulting in decreased visceral/total fat and visceral fat/skeletal muscle ratios.[2] Thus, successful treatment of Cushing disease results in redistribution of adipose tissue that is associated with a reduced cardiovascular risk. However, some cardiovascular risk markers, including C-reactive protein (CRP) and high molecular weight adiponectin, do not seem to normalize despite the restoration of physiologic cortisol concentrations, suggesting that exposure to excess GCs has lasting adverse effects on cardiovascular risk.[2] Furthermore, the increased incidence of the metabolic syndrome and cardiovascular disease seen in Cushing patients may not normalize after remission.[50–52] In fact, the duration of the GC exposure in Cushing disease has been shown to increase the hazard of death in patients even after long-term treatment.[53] Prospective studies are needed to understand whether, despite long-term Cushing remission, previous exposure to GCs will result in elevated trunk and ectopic fat when compared with controls. Persistent obesity and ectopic fat distribution, in turn, could contribute to the elevated mortality risk seen after GC exposure.

GC exposure could enhance lipoprotein lipase (LPL) activity, which mediates the hydrolysis and uptake of circulating triglycerides and FA into adipocytes,[19] and this could occur preferentially in the visceral and trunk subcutaneous adipose tissue depots,[54] although what accounts for this depot-specific LPL activity is unknown. The role of altered lipolytic rates in response to GCs, as previously mentioned, is controversial, although it has been suggested that abdominal depots show reduced lipolysis, which could play a role in their

expansion in humans exposed to chronic GCs.[19] Finally, the GC receptor (GR) α is more highly expressed in visceral than in subcutaneous adipose tissue,[55] and because activation or repression of GC-sensitive genes is mediated by GCs through the GR, differential expression of this receptor is another potential mechanism for preferential accumulation of abdominal adipose tissue.

Accumulation of adipose tissue involves not only hypertrophy of adipocytes but also expansion of the extracellular matrix and nonadipocyte cells, including stromal vascular cells, endothelial cells, monocytes, and macrophages. Obesity and insulin resistance are associated with adipose tissue remodeling, characterized by increases in macrophages (discussed further in the section on anti-inflammatory and diabetogenic actions of GCs), fibrosis, and the extracellular matrix.[56–58] A recent study has demonstrated that on comparison with lean insulin-sensitive subjects, adipose tissue from obese insulin-sensitive individuals had decreased capillary density but larger blood vessels, suggesting a role for altered angiogenesis and oxygen delivery in the setting of obesity.[59] The role of GCs in the regulation of these nonadipocyte components in the adipose tissue in the setting of increasing adipose tissue mass and whole-body insulin resistance has not been investigated, and represents an important area of future research.

GC regulation of the secretory profile of white adipose tissue—Adipokines such as leptin and adiponectin are hormones secreted by adipose tissue that regulate metabolism in other tissues, thereby exerting control of systemic glucose and lipid homeostasis, appetite regulation, and energy expenditure. Leptin levels are elevated in human obesity and diabetes, which are characterized by leptin resistance. Cortisol is known to increase leptin production[60] and high circulating leptin concentrations are seen in patients with active Cushing syndrome, which in turn decrease during remission.[2,61] Cushing remission also reduces the leptin/total adipose tissue and leptin/subcutaneous adipose tissue ratios, but not leptin/visceral adipose tissue ratio, suggesting that the hypercortisolemia in active Cushing syndrome enhances leptin production preferentially in subcutaneous over visceral adipose tissue,[2] consistent with data on healthy individuals showing higher leptin expression in subcutaneous than in visceral adipose tissue.[62]

Adiponectin levels, particularly the biologically more active high molecular weight adiponectin, tightly correlate with insulin sensitivity,[63] and levels and are lower in obesity and diabetes. Values in active Cushing patients were similar to those of nondiabetic healthy women from the Nurses' Health Study[64] and, in contrast to leptin, both high molecular weight[2] and total[42] adiponectin do not change during Cushing remission. GCs reduce adiponectin gene expression,[65] so it is unclear as to why adiponectin does not increase with Cushing remission. A potential explanation could be provided by the observation that in the subcutaneous adipose tissue of rats, corticotropin increases adiponectin gene expression, whereas dexamethasone decreases it.[66] Thus, the elevated circulating corticotropin concentrations that are present during active Cushing disease could counterbalance the effects of GCs on adiponectin secretion.

Cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α can be considered adipokines because they also have systemic metabolic effects. Of importance is that adipose tissue inflammation, which manifests through increased expression of proinflammatory cytokines such as IL-6, IL-1, and TNF-α, and increased infiltration of macrophages in adipose tissue, is believed to play an important role in the pathogenesis of insulin resistance and diabetes. In keeping with their anti-inflammatory actions, GCs decrease adipose tissue inflammatory cytokines ex vivo, which are mainly produced in nonadipocyte cells within the adipose tissue.[67–69] The anti-inflammatory actions of GCs could be another mechanism through which GCs increase insulin sensitivity of adipose tissue in the context of whole-

body insulin resistance.[70] In humans, investigations of the proinflammatory state after GC exposure have been limited to measurement of circulating cytokines, which may or may not reflect the degree of adipose tissue inflammation. A cross-sectional study has demonstrated that patients with active as well as "cured" Cushing syndrome had elevated circulating proinflammatory markers, including soluble TNF-α receptor 1 and IL-6, in comparison with controls, suggesting a persistent state of chronic low-grade inflammation in both active and treated Cushing syndrome,[42] but whether the source of these proinflammatory cytokines is adipose tissue remains to be determined. Furthermore, whether exogenous or endogenous GCs reduce adipose tissue inflammation in an obese insulin-resistant individual is presently not known. In fact, some in vitro data suggest that GCs restrain the lipolytic effects of inflammatory cytokines produced in adipose tissue. Specifically, the addition of dexamethasone to cultured adipocytes blocked the induction of lipolysis and insulin resistance induced by TNF-α treatment.[15] In contrast to these data, however, one 11β-HSD1 inhibitor currently in development was found to decrease adipose tissue expression of TNF-α and macrophage infiltration,[71] suggesting that limiting adipose tissue GC exposure could prevent the inflammation that occurs with the development of obesity. These apparent contradictions again are likely explained by the complex physiology of GC action in vivo, in particular by the many secondary effects that occur through altered metabolism and insulin action induced by GCs.

GC regulation of brown adipose tissue—In contrast to white adipose tissue, brown adipose tissue primarily functions as a thermogenic tissue through uncoupled β-oxidation.[72] Murine data show that increasing brown adipose tissue can enhance energy expenditure and reduce adiposity.[73] Accordingly, brown adipose tissue ablation promotes the development of an obese phenotype in response to high-fat diets.[74] In contrast to previous belief, recent studies using positron emission tomography combined with computed tomography have shown the presence of brown adipose tissue in adult humans in the paracervical and supraclavicular region[75–77]; thus, its potential role in metabolism and energy homeostasis has gained recent attention. GCs have been shown to downregulate expression of mitochondrial uncoupling protein 1 (UCP-1), which is the protein that confers the exceptional thermogenic capacity and the ability to uncouple β-oxidation from adenosine triphosphate production in brown adipose tissue. Transgenic mice that overexpress 11β-HSD1 selectively in white adipose tissue had decreased UCP-1 expression in the interscapular brown adipose tissue.[54] Both pharmacologic 11β-HSD1 inhibition and genetic knockout of 11β-HSD1 lead to increased expression of brown adipose tissue–specific genes, whereas overexpression of 11β-HSD1 in mice leads to decreased expression of these genes in brown adipose tissue.[78] These data suggest that GCs reduce the function of brown adipose tissue, while 11β-HSD1 inhibition could represent a therapeutic strategy to increase such function and prevent obesity.

Mechanisms of GC-Induced Insulin Resistance in Muscle

The ability of GCs to increase insulin sensitivity of adipose tissue contrasts with their effects on muscle where GCs decrease insulin-mediated glucose uptake. As shown in primary cell culture and cell lines, this may occur via stimulation of serine kinases, resulting in phosphorylation and inactivation of IR and IRS molecules.[27,79] Accumulation of intramyocellular lipids (droplets of triglyceride in skeletal muscle fibers) is similarly associated with insulin resistance.[80–84] Thus, intramyocellular lipid accumulation is thought to represent an early defect in the development of type 2 diabetes mellitus.[85] Excessive accumulation of intramyocellular lipid could represent another mechanism by which GCs affect metabolism, but as yet it remains unclear as to whether this occurs during GC exposure in humans. However, a recent study using cell lines and rodent models demonstrated that GCs dysregulate lipid metabolism in skeletal muscle by enhancing β-

oxidation and lipolysis.[86] Furthermore, inhibition of 11β-HSD1, which is expressed in muscle,[79] decreased lipogenic and lipolytic gene expression. Thus, GCs regulate both carbohydrate and lipid metabolism in skeletal muscle, which could play an important role in regulating muscle and whole-body insulin sensitivity.

Another recently characterized ectopic adipose depot is called intermuscular adipose tissue, which should not be confused with the already described intramyocellular lipid, and is defined as fat that is located beneath the muscle fascia but between the muscle groups (ie, fat "marbling" within the muscle). Intermuscular adipose tissue has been associated with development of insulin resistance,[87] but was not found to be different in patients with Cushing disease in comparison with weight-matched controls,[1] nor decreased after remission[2] when measured by whole-body MRI.

Although a direct relationship between GC-induced skeletal muscle atrophy and development of insulin resistance in muscle has not been established, myopathy is another well-described adverse consequence of GC exposure. In humans with Cushing syndrome, skeletal muscle mass is reduced in comparison with weight-matched controls.[1] Surprisingly, skeletal muscle mass continued to decrease significantly over time after surgical remission, possibly in part related to the weight loss that these patients experience (which results in loss of both fat and lean tissue). Of note, the skeletal muscle mass in remission was inversely correlated with duration of oral GC exposure, suggesting that even exposure to physiologic-range exogenous GCs may have an effect on reducing skeletal muscle mass. This finding underscores the gap in knowledge surrounding what constitutes the least amount of GC exposure, in both dose and duration, that will not result in adverse body composition and metabolic consequences.

Mechanisms of GC-Induced Hepatic Insulin Resistance: Lipogenesis, Steatosis, and Circulating Lipids

Intrahepatic lipids have been shown to be associated with insulin resistance and obesity, and to represent an important marker of cardiovascular risk, possibly even more so than visceral fat.[80–84,88] Several mechanisms have implicated GCs in the stimulation of hepatic lipogenesis and insulin resistance. GCs enhance insulin-stimulated hepatic lipogenesis by upregulation of acetyl-CoA carboxylase and FA synthase.[89,90] GCs also increase very low-density lipoprotein (VLDL) production and secretion because of inhibition of hepatic lipolysis.[91] Several indirect mechanisms also likely play a role in the accumulation of hepatic lipids in response to GCs, including accumulation and lipolysis of visceral adipose tissue, with delivery of free FA to the liver, and systemic hyperinsulinemia and hyperglycemia, which drive hepatic de novo lipogenesis.[92] Finally, GCs induce hepatic insulin resistance by stimulating hepatic gluconeogenesis via induction of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase. The critical role of GCs in hepatic lipid metabolism is demonstrated in vivo by improvements in hepatic steatosis and normalization of hepatic triglyceride concentrations in a fatty liver mouse model after liver-specific GR disruption.[93]

Clinical data implicating GCs in the pathogenesis of hepatic steatosis are limited, however. Obese patients with hepatic steatosis (quantified by ultrasonography) had higher post–dexamethasone-suppressed cortisol values compared with patients without steatosis,[94] and altered cortisol metabolism has been shown in patients with hepatic steatosis,[95–97] suggesting a relationship between hepatic fat and altered cortisol sensitivity and regulation in the general population. Although the development of hepatic steatosis is recognized as a sequela of chronic excess GC exposure in humans, only one report has demonstrated hepatic steatosis in Cushing syndrome by computed tomography,[98] and only a few clinical reports have described the effect of exogenous GCs to promote hepatic steatosis.[99,100] Intrahepatic

lipid as assessed by ^{1}H-magnetic resonance spectroscopy, the gold standard for assessing hepatic lipid, has never been investigated in states of chronic GC exposure in humans. Thus, while existing data suggest a role for GCs in the development and progression of hepatic steatosis and its metabolic consequences, this proposal needs to be confirmed in clinical studies.

GC Regulation of Circulating Lipids

It is widely recognized that GCs result in dyslipidemia, although good-quality clinical data characterizing the prevalence and degree of lipid abnormalities are lacking. Surprisingly, a large survey of patients exposed to exogenous GCs did not show an association with an adverse lipid profile; in fact, higher HDL levels were seen in patients older than 60 years.[101] In keeping with this finding, daily low-dose dexamethasone given to healthy people for 3 weeks increased HDL cholesterol.[102] By contrast, an association between GC exposure and triglyceride, total cholesterol (TC), and low-density lipoprotein (LDL) concentrations was seen in a large cohort of hypopituitary patients on replacement GCs.[103] Some data suggest that corticotropin itself exerts hypolipidemic effects, introducing the potential importance of the route of GC exposure (eg, endogenous vs exogenous) and suggesting that hyperlipidemia in individuals treated with GCs may in part result from corticotropin deficiency, in addition to GC excess.[104–106]

In active Cushing syndrome dyslipidemia has been described, possibly as a result of an increase in VLDL and LDL but not HDL, resulting in an elevation of triglyceride and TC.[51,107,108] Accordingly, morning plasma cortisol and cortisol concentration after low-dose dexamethasone correlated with TC and LDL cholesterol in a series of patients with active Cushing syndrome.[109] However, one report did not find reduced HDL-cholesterol concentrations in active Cushing syndrome,[109] and in another series mean TC/HDL and LDL/HDL values were in the desirable range (<4.5 for TC/HDL and <3.0 for LDL/HDL) in active disease.[2] Furthermore, a prospective study of patients with Cushing disease studied before and over time after surgical remission demonstrated a decrease in only TC, whereas LDL, HDL, triglyceride, and the ratios (TC/HDL and LDL/HDL) did not change.[2] In fact, HDL decreased in 11 of the 14 patients, but the mean change was not significant.[2] Other longitudinal Cushing studies have also not shown a change in lipid profile with remission.[51,108] The fact that many Cushing patients remain either overweight or obese despite remission could play a role in the lack of change in the lipid profile.[2] These findings also suggest the possibility that GC exposure has lasting effects on lipid profiles even after eucortisolism has been restored.

Potential Effects of Brain GCs on Metabolic Homeostasis

An understanding of the role of brain GCs in whole-body metabolic homeostasis is needed, in part given the widely prevalent use of nasal GCs, which potentially could, depending on the formulation and dose, result in central nervous system (CNS) GC exposure via transport along the olfactory and trigeminal nerve fibers, although this is yet to be studied specifically for GCs. A few studies have suggested a role for brain GCs in the regulation of metabolic homeostasis, although data are still very limited in this area.

Brain GC levels are a function of GC uptake and local GC activation through 11β-HSD1, which is present in hippocampal neurons as well as neurons in the hypothalamic arcuate and paraventricular hypothalamic nuclei.[110–112] A recent human brain-bank study found wide expression of 11β-HSD1 mRNA in the suprachiasmatic nucleus, which is the biological clock of the brain, as well as the supraoptic, paraventricular, and infundibular nuclei. In the paraventricular nucleus, neuronal 11β-HSD1 immunoreactivity colocalized with corticotropin-releasing hormone, suggesting that modulation of brain GC availability could

play a role the in regulation of the HPA axis with regard to metabolism, appetite, and circadian rhythms.[113]

Several central and peripheral GC effects are mediated via neuropeptide Y (NPY), which is an abundantly expressed peptide involved in the regulation of the stress response, including appetite, anxiolysis, and vasoconstriction. Animal studies have shown that central (intracerebroventricular) administration of dexamethasone enhances NPY content in the arcuate nucleus of the hypothalamus, a key regulator of the HPA axis, and results in hyperphagia, hyperinsulinemia, insulin resistance, and weight gain in rats.[114,115] Specifically, using euglycemic-hyperinsulinemic clamps, continuous central dexamethasone infusion resulted in weight gain and insulin resistance, manifested by decreased insulin-stimulated glucose utilization.[114,116] These effects were shown to be mediated by the activation of the parasympathetic nervous system, as they were abolished in vagotomized animals.[116] Another study demonstrated that hypothalamic GC action modulates hepatic insulin sensitivity via NPY and the sympathetic nervous system.[117] In the periphery, excess GCs caused by chronic stress in mice upregulated the expression of NPY in sympathetic neurons and the expression of its receptor on abdominal adipocytes, leading to angiogenesis and adipogenesis, thus contributing to the development of abdominal obesity and insulin resistance.[118]

Another potential mechanism for many GC-induced effects is through tissue-specific regulation of adenosine monophosphate–activated kinase (AMPK), a regulator of cellular and systemic energy homeostasis, which acts through enzyme phosphorylation and regulation of gene and protein expression.[119,120] Activation of hypothalamic AMPK may be associated with an increase in appetite, whereas in adipose tissue it may inhibit lipogenesis. One study demonstrated reduced adipose tissue AMPK activity in insulin-resistant subjects in comparison with insulin-sensitive individuals.[121] In the liver, AMPK activation is suggested to play a role in inhibiting gluconeogenesis and FA and cholesterol synthesis. A recent study using a rat model of Cushing showed that GC treatment was associated with inhibition of AMPK activity in the adipose tissue and heart, but with stimulation in the liver and hypothalamus. Similar activity patterns were observed in vitro in adipose, hypothalamic, and liver cells. These data suggest that GC-induced changes in AMPK could underpin the increase in appetite, the accumulation of visceral and hepatic fat, and the cardiovascular risk that characterizes GC excess.[122] Furthermore, the regulation of AMPK through GCs may occur, at least in part, via endocannabinoids and their cognate receptor cannabinoid receptor 1 (CB1), a widely expressed receptor in the CNS and the hypothalamus, but which is also present at low levels in adipose tissue, liver, and muscle.[123] In the hypothalamus, activation of CB1 is associated with appetite stimulation, whereas in adipose tissue it may increase lipogenesis.[124] GC stimulation of endocannabinoid tone in the hypothalamus[125,126] also altered hypothalamic AMPK,[122] and this may be dependent on the CB1 receptor because GC-treated CB1 knockout mice did not gain weight in the setting of a lack of increase in hypothalamic and hepatic AMPK.[127] Whether the effects of GCs indicate a specific role of CB1, or if the reduced weight gain after GCs is secondarily due to the impaired ability of CB1 knockout mice to gain weight in a variety of settings, for example if they fail to gain weight on a high-fat diet or in the setting of genetic leptin deficiency,[128] is unclear.

11β-HSD1 AS A GATEKEEPER FOR INTRACELLULAR GC AVAILABILITY

Intracellular GC availability is regulated by the activity of 11β-HSD1, a widely expressed NADP(H)-dependent enzyme that acts predominantly as a reductase in vivo to convert inactive cortisone to cortisol.[129–135] Tissue-specific actions of 11β-HSD1 are shown in Table 1. Overexpression of 11β-HSD1 in the adipose tissue of mice promotes abdominal obesity, insulin resistance, hepatic steatosis, and elevated circulating free FA and

triglyceride concentrations.[54,136] Similarly, in vitro studies have shown that 11β-HSD1 inhibition reduces adipogenesis in human adipose cells.[137] Knockout of 11β-HSD1 in mice improves hepatic insulin action and results in a phenotype that is resistant to overfeeding-induced obesity and diabetes.[138–141]

As liver is the site of highest 11β-HSD1 expression and a major cortisol producer,[134,135,142,143] liver-selective 11β-HSD1 disruption has profound effects on whole-body metabolism, resulting in HPA-axis activation and adrenal hypertrophy.[144] Similar to that seen in adipose tissue, overexpression of 11β-HSD1 in the liver is associated with hepatic steatosis, insulin resistance, and elevated TC and triglyceride levels.[145,146] In fact, an animal model of obesity and the metabolic syndrome had increased hepatic (but reduced adipose tissue) 11β-HSD1 levels,[147] suggesting a possible role for selective hepatic 11β-HSD1 inhibition to reduce GC-mediated hepatic glucose output.[148] However, although some murine liver-specific knockout models of 11β-HSD1 lack significant metabolic abnormalities, highlighting the important compensatory role of HPA-axis activation and extrahepatic 11β-HSD1 activity,[144] these mice are protected from the obesity and insulin resistance that develop in the setting of chronic 11-dehydrocorticosterone administration.[149]

In humans, local production of excess GCs by upregulation of 11β-HSD1 in abdominal adipose tissue[131,150,151] has been suggested to cause visceral adiposity and the metabolic syndrome,[132,133] as 11β-HSD1 activity is higher in visceral than in subcutaneous adipose stromal cells,[134,142] and higher in adipose tissue from obese subjects compared with lean controls.[130,152] Studies in obesity and diabetes, however, are mixed, with both similar[153–157] and increased[130,151,158–161] adipose tissue 11β-HSD1 expression in obese diabetics when compared with lean insulin-sensitive individuals. Human obesity may be associated with decreased hepatic 11β-HSD1 activity, which is speculated to be a compensatory mechanism aimed to decrease hepatic glucose output and preserve insulin sensitivity.[54,162,163] By contrast, decreased 11β-HSD1 activity was not demonstrated in patients with diabetes, suggesting that higher cortisol hepatic exposure could contribute to the progression to diabetes in some obese individuals.[156]

Expression of 11β-HSD1 is increased by GCs and insulin.[164] However, patients with Cushing syndrome had levels of 11β-HSD1 mRNA similar to those of lean controls and lower than those of obese individuals, possibly because of downregulation from chronic hypercortisolemia.[151,165] 11β-HSD1 expression is also induced by leptin and proinflammatory cytokines. Thus, the increases in local or systemic proinflammatory cytokines seen in obesity may further enhance adiposity by increasing 11β-HSD1 expression and local generation of GCs.

The Potential Role of 11β-HSD1 Inhibition in Humans

11β-HSD1 inhibition is a potentially promising novel therapeutic approach to the treatment of obesity and diabetes. In healthy people, carbenoxolone (a nonselective 11β-HSD inhibitor) improves whole-body insulin sensitivity[166]; in diabetic subjects, it decreases production rates of hepatic glucose during hyperinsulinemic-euglycemic clamp but does not augment glucose disposal.[167] Carbenoxolone has also been shown to limit GC-induced lipolysis in subcutaneous fat[168] and decrease circulating TC.[167] These data have provided a rationale for the development of selective 11β-1HSD1 inhibitors.

In rodent models, inhibition of 11β-HSD1 improves insulin sensitivity; decreases hepatic steatosis and the expression of the hepatic gluconeogenic enzymes PEPCK and glucose-6-phosphatase; reduces TC, free FA, and triglycerides; and results in a phenotype that is resistant to obesity and diabetes.[140,169–175] A confounding factor is the reduction in food intake seen in many studies, which could be due to nonspecific toxic effects of these

compounds. However, some studies have shown similar results with pair-fed groups,[79] supporting the notion that 11β-HSD1 inhibition improves insulin action that at least in part is independent of alterations in caloric intake.

Initial studies in humans have been encouraging. One compound, which has been administered to diabetic patients in combination with metformin, was shown to have beneficial effects on weight, lipid profile, and glycemic control.[176] However, another compound had more modest beneficial effects on glycemic control and, despite a moderate decrease in weight, increased both LDL and HDL concentrations.[177] Some compounds also lower blood pressure.[178] Concerns regarding clinical use of 11β-HSD1 inhibitors include compensatory HPA-axis upregulation, resulting in adrenal hypertrophy and corticotropin-driven excess of adrenal androgen.[179] Additional effects on the immune system, such as whether 11β-HSD1 may play a role in limiting the acute inflammatory response, are unknown, as are effects of longer-term treatment in humans. The magnitude of the effect of inhibition in humans is also questionable, as there may be species differences in the extent of the role of GC metabolism in obesity and metabolic disease.

THE ROLE OF GCS IN THE DEVELOPMENT OF COMMON OBESITY

Given the striking phenotypic and metabolic similarities between so-called common obesity (and associated insulin resistance) with Cushing syndrome, endogenous GCs have been implicated in the pathogenesis of this condition. However, data are limited by variability of serum and urine cortisol measures and their lack of reflection of true cellular and tissue GC action. Subtle GC abnormalities, including reduced endogenous cortisol suppression to dexamethasone[180,181] and tissue-specific alterations in cortisol metabolism,[150,152] have been associated with obesity and insulin resistance. The abdominal obesity phenotype, in particular, may be associated with alterations in GC activity,[182,183] as well as increased cortisol response to food and other HPA-axis stimulators including corticotropin, vasopressin, and corticotropin-releasing hormone.[184–188] Other abnormalities, including higher salivary cortisol level in response to stress,[189,190] different GR polymorphisms,[191–193] and chronic low-dose oral GCs,[103] have also been associated with obesity, higher waist circumference,[194,195] insulin resistance, the metabolic syndrome, and increased mortality. A recent study showed that long-term elevations in cortisol, measured in scalp hair, were associated with higher risk for diabetes, cardiovascular disease,[196] and the metabolic syndrome among community dwellers.[197] However, some studies show decreased salivary and serum cortisol levels in obesity; moreover, circulating GC concentrations and their response to stimulation or suppression are well known to be variable, and often do not predict their effects or function in target tissues.[198] Thus, the mechanisms for altered GC activity, and the precise tissue and cellular actions of GCs in obesity and metabolism, need further elucidation. As circulating cortisol is normal in obesity, further work should also explore the role of local tissue GC exposure via 11β-HSD1, and alterations in HPA-axis sensitivity and circadian rhythm in the pathogenesis of obesity.

THE PARADOX OF GC ANTI-INFLAMMATORY YET DIABETOGENIC ACTIONS: DURATION, LOCATION, OR CONTEXT?

Inflammation of white adipose tissue is believed to play an important role in the development of obesity-related adverse metabolic sequelae.[70,199] Chronic activation of proinflammatory pathways within white adipose tissue and other insulin target tissues may impair metabolic control, possibly by impairing insulin signaling. For instance, adipocytes from obese individuals exhibit higher basal lipolysis,[200] in part because of elevated TNF-α,[201] an inflammatory cytokine that can impair insulin signaling through serine

phosphorylation of IRS proteins.[202] Lipolysis results in the release of free FA which, in turn, leads to macrophage infiltration of adipose tissue.[203,204] Thus, a popular exemplar of how obesity leads to insulin resistance is that inflammation within adipose tissue causes insulin resistance, and increases the risk for atherosclerosis and cardiovascular events.[7,8] By contrast, GCs have potent anti-inflammatory and immunosuppressive actions, and as such are used to treat states of abnormal immune activation, including many autoimmune and rheumatologic diseases. GCs suppress proinflammatory cytokine expression in vitro[205–207] and in vivo,[208] with the most pronounced effect on TNF-α and the least effect on IL-6.[209] States of chronic GC excess consistently predispose patients to the adverse effects of immune suppression, such as the increased fungal infections seen in Cushing syndrome.[210] It might follow that Cushing syndrome would be characterized by a lower degree of inflammation, in particular adipose tissue inflammation, thereby reducing insulin resistance and improving metabolic regulation. Clinically, however, Cushing syndrome induces glucose intolerance, dyslipidemia, and cardiovascular mortality, all of which are usually associated with inflammation, suggesting that chronic in vivo exposure to GCs may in fact result in systemic inflammation.[6,51,211,212] Thus, there is a paradox between the anti-inflammatory properties of GCs and their dysmetabolic effects, which presents an important caveat to the prevailing model of inflammation as an important link between obesity and insulin resistance.

The effects of chronic GC exposure attributable to Cushing syndrome on proinflammatory mediators have not been well studied. IL-1β, IL-6, and TNF-α levels in female patients with Cushing syndrome were not different compared with those in controls,[213] although acute elevations in these cytokines were observed in the immediate postoperative hypocortisolemic period. Whether the latter observation is due to the hypocortisolism rather than the preceding stress of surgery is unclear. Other studies have shown elevated circulating cytokines in both active[214] and treated[42] patients with Cushing syndrome in comparison with controls, including elevated CRP, IL-6, and TNF-α concentrations, with increased endothelin-1 after insulin bolus and reduced basal and stimulated nitric oxide release, suggesting an increased proatherogenic risk profile in addition to increased inflammatory markers in Cushing syndrome.[214] Furthermore, IL-1 receptor antagonist was found to be high in active Cushing syndrome and decreased after surgery, in association with decreased fat, particularly trunk fat (quantified by dual-energy x-ray absorptiometry).[215] Whether this represents a relationship between body composition and markers of inflammation in Cushing syndrome requires further supportive data. Future studies will need to clarify the chronic effects of hypercortisolemia on serum and adipose tissue inflammatory cytokines, and correlate this inflammatory profile with measures of insulin action and cardiovascular risk. Whether the anti-inflammatory actions of GCs are duration dependent or tissue dependent will be an important area of future investigations.

SUMMARY AND FUTURE DIRECTIONS

GCs are critical in the regulation of energy homeostasis, in large part owing to their control of lipid metabolism and adipose tissue function. Although physiologic exposure to GCs and a dynamic HPA axis that is responsive to metabolic and environmental cues are essential for the survival of any organism, chronic exposure to even subtle GC excess cause adverse sequelae, including the development of excess abdominal and ectopic adipose tissue, dyslipidemia, cardiovascular disease, and, ultimately, shorter survival. Prevalent forms of subtle GC excess include exogenous exposure, which is widely used in the treatment of autoimmune and rheumatologic diseases, and chronic stress with resultant activation of the HPA axis. Even common obesity and the metabolic syndrome have been proposed as models of excess endogenous GCs, through enhanced HPA-axis activation, altered metabolism, and/or a flattened cortisol circadian rhythm.

Thus, the study of GC regulation of insulin action and lipid metabolism in target organs is of critical importance. Further investigation is needed to address critical gaps in our understanding of the regulation of GCs on adipose tissue function. First, the effects of prolonged versus acute in vivo GC exposure on insulin action in adipose tissue need further exploration, including investigation of the effects of GC-induced systemic hyperinsulinemia and insulin resistance on adipose tissue function. Second, while some studies have suggested that the post-hypercortisolemic state is associated with persistent adverse metabolic and cardiovascular risk, the extent and precise mechanisms of these abnormal patterns, at both the systemic and tissue levels, have not been delineated. Third, the paradox of GC anti-inflammatory yet diabetogenic effects, and the investigation of serum and tissue markers of inflammation in the context of obesity and insulin resistance need clarification. Finally, further knowledge of the underpinnings of GC effects on adipose tissue and metabolic function will provide a rationale for new GC therapeutic agents with enhanced beneficial (eg, anti-inflammatory) but reduced adverse (eg, diabetogenic and adipogenic) effects.

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KEY POINTS

- Glucocorticoids (GCs) are critical in the regulation of energy homeostasis, and liberate energy substrates for mitochondrial oxidation during stress by enhancing muscle protein breakdown, adipose tissue lipolysis, hepatic gluconeogenesis, and reducing glucose utilization, all of which elevate circulating glucose concentrations.
- Chronic excessive glucocorticoid exposure results in whole-body insulin resistance and the development of abdominal adiposity in humans.
- The ability of GCs to induce adipose tissue lipolysis depends on their concentration, duration of exposure, and the specific adipose tissue depot.
- 11β-Hydroxysteroid dehydrogenase 1 is a gatekeeper for intracellular GC availability through the local activation of GCs within tissues.
- Prevalent forms of subtle GC excess include exogenous exposure as treatment of auto-immune and rheumatologic diseases, or chronic stress with resultant activation of the hypothalamic-pituitary-adrenal axis.

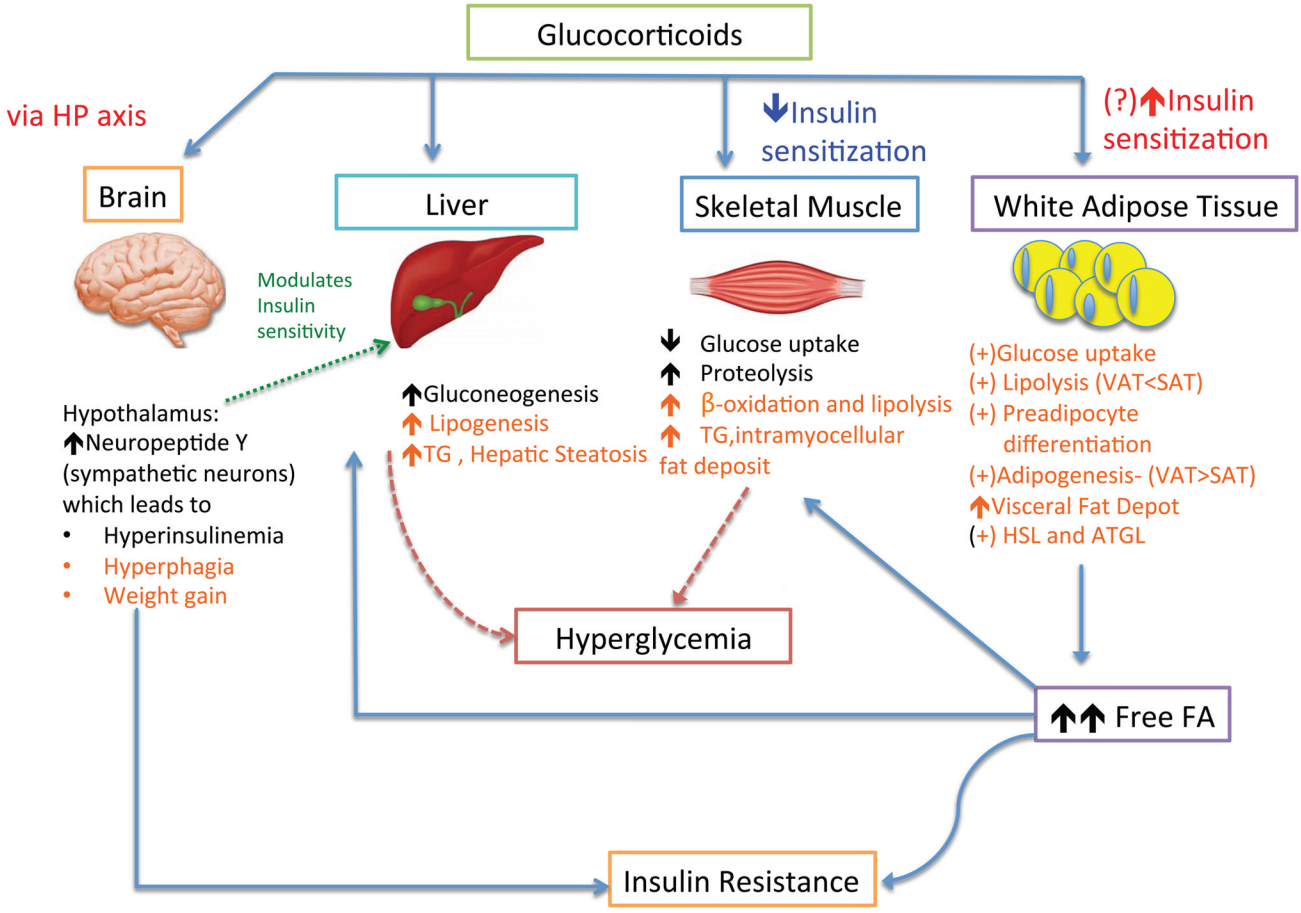

Fig. 1.

GCs promote whole-body insulin resistance via visceral adipogenesis, mobilization and release of free fatty acids into the circulation, and development of hepatic steatosis. Whereas in muscle GCs impair insulin action, they may enhance insulin action in adipose tissue, thus promoting expansion of adipose tissue. ATGL, adipose triglyceride lipase; FA, fatty acids; HP, hypothalamic-pituitary-adrenal; HSL, hormone-sensitive lipase; SAT, subcutaneous adipose tissue; TG, triglycerides; VAT, visceral adipose tissue.

Table 1

Tissue-dependent actions of 11β-hydroxysteroid dehydrogenase 1

Tissue	Overexpression	Inhibition or Knockout
White adipose tissue	Hyperglycemia and insulin resistance Dyslipidemia: elevated circulating TG and FA Increased adiposity: visceral > subcutaneous adipose tissue	Enhanced insulin sensitivity Improved hepatic insulin action Decreased TG and FA Resistance to development of obese phenotype
Brown adipose tissue	Decreased UCP-1 expression	Increased UCP-1 expression
Liver (highest expression)	Insulin resistance Elevated circulating TC and TG Hepatic steatosis Stimulation of HPA axis leading to adrenal hypertrophy	Increased hepatic insulin action Decreased fasting glucose and glucose output Decreased expression of gluconeogenic enzymes PEPCK and G6P
Brain	Expression seen in hippocampus and hypothalamus, suggesting a role in the regulation of metabolism and appetite	Needs further exploration
Muscle	Needs further exploration	Decreased lipogenic and lipolytic gene expression

Abbreviations: FA, fatty acids; G6P, glucose-6-phosphatase; HPA, hypothalamic-pituitary-adrenal; PEPCK, phosphoenolpyruvate carboxykinase; TC, total cholesterol; TG, triglyceride; UCP-1, mitochondrial uncoupling protein 1.