METABOLISM CLINICAL AND EXPERIMENTAL 60 (2011) 1500–1510

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Metabolism

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Review

The effects of glucocorticoids on adipose tissue lipid metabolism

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ARTICLE INFO

Article history:
Received 5 May 2011
Accepted 18 June 2011

ABSTRACT

Glucocorticoids (GCs) have long been accepted as being catabolic in nature, liberating energy substrates during times of stress to supply the increased metabolic demand of the body. The effects of GCs on adipose tissue metabolism are conflicting, however, because patients with elevated GCs present with central adiposity. We performed an extensive literature review of the effects of GCs on adipose tissue metabolism. The contradictory effects of GCs on lipid metabolism occur through a number of different mechanisms, some of which are well defined and others remain to be elucidated. Firstly, through increases in caloric and dietary fat intake, along with increased hydrolysis of circulating triglycerides (chylomicrons, very low-density lipoproteins) by lipoprotein lipase activity, GCs increase the amount of fatty acids in circulation, which are then available for ectopic fat distribution (liver, muscle, and central adipocytes). Glucocorticoids also increase de novo lipid production in hepatocytes through increased expression of fatty acid synthase. There is some controversy as to whether these same mechanisms occur in adipocytes, thereby contributing to adipose hypertrophy. Glucocorticoids promote preadipocyte conversion to mature adipocytes, causing hyperplasia of the adipose tissue. Glucocorticoids also have acute antilipolytic effect on adipocytes, whereas their genomic actions facilitate increased lipolysis after about 48 hours of exposure. The acute and long-term effects of GCs on adipose tissue lipolysis remain unclear. Although considerable evidence supports the notion that GCs increase lipolysis through glucocorticoid-induced increases of lipase expression, they clearly have antilipolytic effects within these same tissues and cell line models.

1. Introduction

Adipose tissue plays an important regulatory role in normal substrate metabolism by storing and liberating high-energy compounds when the body requires them. During times when food is plentiful and physical activity level is low, excess energy is stored within adipose tissue in the form of triglycerides. When an energy deficit occurs, such as during fasting or exercise, triglycerides are broken down; and fatty acids (FAs) and glycerol are released into circulation. This release helps to supply the organism's increased energy demands. Balance usually exists between these 2 states; but dysregulation can occur, leading to either an excessive storage of lipid within adipose tissue or an excessive depletion in states of catabolism. One of the key regulators of energy flux within adipocytes are the stress hormones; glucocorticoids

Author contributions: This paper was written by AJ Peckett and edited by MC Riddell and DC Wright.

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0026-0495/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2011.06.012

(GCs) (ie, cortisol in human, corticosterone in rodents); catecholamines (ie, epinephrine, norepinephrine); and, in some stressful situations, growth hormone (GH). In humans [1] and in rodents [2], stress and/or stress hormones have been widely cited as contributing to excess adiposity, either by altering food intake or by influencing the storage of FAs, despite the observations that these hormones clearly have lipolytic actions in isolated conditions [3]. Understanding the effects of stress hormones on the regulation of adipose tissue metabolism is critical in determining why these clinical links between stress and/or stress hormones and excess adiposity exist. This review highlights the physiological regulation of adipose tissue metabolism by the stress hormones, with a focus on the effects of GCs.

2. Stress and hypothalamic-pituitary-adrenal axis activation

Regardless of whether a stressor is psychological or physiological in nature, the body responds in much the same way. The brain perceives the stressor and initiates a signaling cascade that results in the release of GCs and epinephrine from the adrenal gland. Catecholamines are released from the adrenal medulla as a result of direct sympathetic innervation, whereas activation of the hypothalamic-pituitary-adrenal (HPA) axis results in GC release primarily from the zona fasciculata region of the cortex. The HPA axis is activated when a stressor is perceived, and the response begins with the release of corticotropin-releasing hormone from the paraventricular nucleus in the hypothalamus. The corticotropin-releasing hormone travels to the anterior pituitary where it stimulates the release of corticotropin. The binding of corticotropin to receptors in the adrenal cortex induces GC synthesis and release into the systemic circulation.

Although GCs and catecholamines are the primary hormones released during times of stress, the secretion of other hormones, such as prolactin, GH, and thyrotropin, is also altered in response to certain types of stressors; for example, GH is released in response to exercise and hypoglycemia, but is not released in response to psychological stress [4] and is decreased with prolonged psychosocial stress [5]. The importance of the release of these other hormones/products during stress is less clear but may be related to increased energy provision in the face of hypoglycemia or during exercise [4].

The release of stress hormones allows the body to maintain homeostasis during times of stress [6]. When a stressor arises, most tissues increase their metabolic needs (skeletal and cardiac muscle, central nervous system, lungs, vasculature, etc); and thus, the energy demands of the body are dramatically elevated. Stress hormones act to supply this energy, as they liberate energy substrates such as glucose, amino acids, glycerol, and FA. This catabolic action in the stimulated state is thought to be the typical function of stress hormones. Whereas catecholamines have immediate effects of short duration, the effects of GCs are classically thought to take hours to appear and last for a much longer duration [7]. Catecholamines mediate their effects by binding to G-protein–coupled receptors (α- and β-adrenergic type) on the cell membrane. This binding initiates an intracellular signaling cascade and allows for their immediate effects. Glucocorticoids' long-term effects are thought to be mediated through the GC receptors (GRs) in each tissue, which activate or repress gene transcription [8]. By altering protein expression, these "genomic" effects of GCs take time to develop and will last even when the hormone is no longer present [9]. Whether GCs also have short-term, nongenomic effects on substrate mobilization is not entirely clear, although evidence is emerging that they likely do, at least in the central nervous system [10]. Although typically anabolic in nature, GH have some catabolic effects (eg, increasing adipose tissue lipolysis, promoting liver and/or muscle glycogenolysis) during certain types of stress (ie exercise, hypoglycemia) by enhancing the catecholamine actions on β-adrenergic activity [11]. Overall, the combined catabolic actions of stress hormones allow the release of energy substrates and aid the body in maintaining fuel homeostasis.

3. Adipose tissue lipolysis

In terms of the adipose tissue, a great deal of research has focused on stress hormones' effects on lipid breakdown. Lipolysis, the breakdown of stored lipids, is governed largely by the lipase enzymes that control the stepwise breakdown of triglycerides (Fig. 1). Lipids are stored in the adipose tissue as triacylglycerol (TAG), also referred to as *triglycerides*, and are composed of 3 fatty acids attached to a glycerol backbone. Lipases break down TAGs and result in the liberation of FAs and the glycerol molecule. With the removal of one FA, TAGs are converted to the lipid intermediate diacylglycerol; and with the removal of 2 FAs, they become monoacylglycerol. Adipose triglyceride lipase (ATGL) is predominantly responsible for the conversion of TAGs to diacylglycerol and the release of one FA, the first step of lipolysis, and may be the rate-limiting enzyme [12]. Hormone-sensitive lipase (HSL) is also capable of breaking down TAGs to diacylglycerol, but to a lesser extent than ATGL; and HSL's primary function involves the conversion of diacylglycerol to monoacylglycerol. In the basal state, HSL is found in the cytoplasm and has little lipolytic activity. In the stimulated state, however, HSL translocates to the lipid droplet and is able to have a great impact on lipolysis (the details of stimulated lipolysis will be discussed further below). Monoacylglycerol lipase is involved in the final stage of lipolysis and is responsible for the breakdown of monoacylglycerol to glycerol and the third FA.

As mentioned previously, GCs are believed to mediate many of their effects by altering gene transcription through their interaction with the GR [8], although direct nongenomic effects on lipolysis have also been recently proposed [13]. Much of the literature agrees that GCs increase lipolysis in mature adipocytes as a result of increased transcription and expression of the lipase proteins ATGL and HSL [3,13-15]. Elevated levels of GCs in circulation or in specific adipose depots would then be expected to increase the breakdown of lipids. Because of the time it takes for transcription and protein expression to occur, these effects are not seen

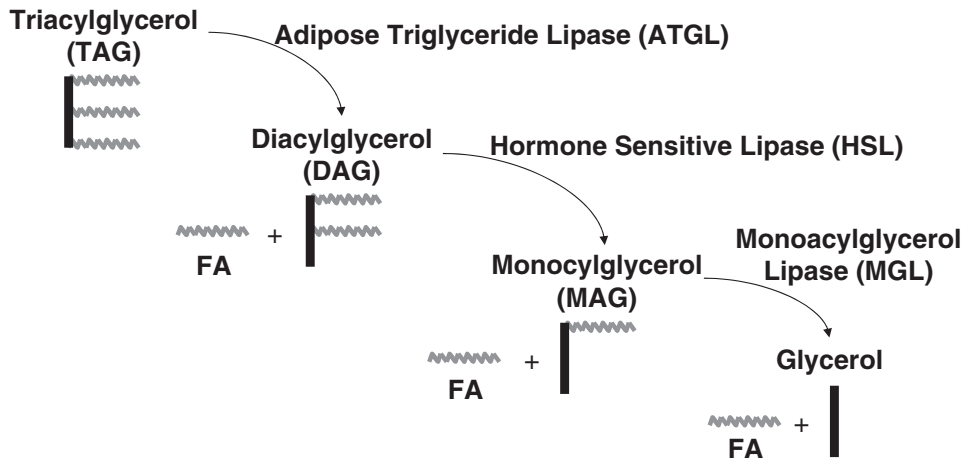

Fig. 1 – The breakdown of TAG during lipolysis. The lipase enzymes ATGL, HSL, and monoacylglycerol lipase are responsible for the stepwise breakdown of TAG and the liberation of FAs and glycerol.

immediately; and thus, increases in basal lipolysis do not occur until hours or days after GC exposure [9,15].

There are also many upstream regulators of lipolysis that can affect the efficiency of these lipases. Modification to these regulators is largely how catecholamines have their potent lipolytic effects. The β-adrenergic pathway is one of the more well-defined pathways regulating lipolysis (Fig. 2). Catecholamines bind to β-adrenergic receptors and initiate a signaling cascade that increases the activity of adenylyl cyclase and results in increased cyclic adenosine monophosphate (cAMP)

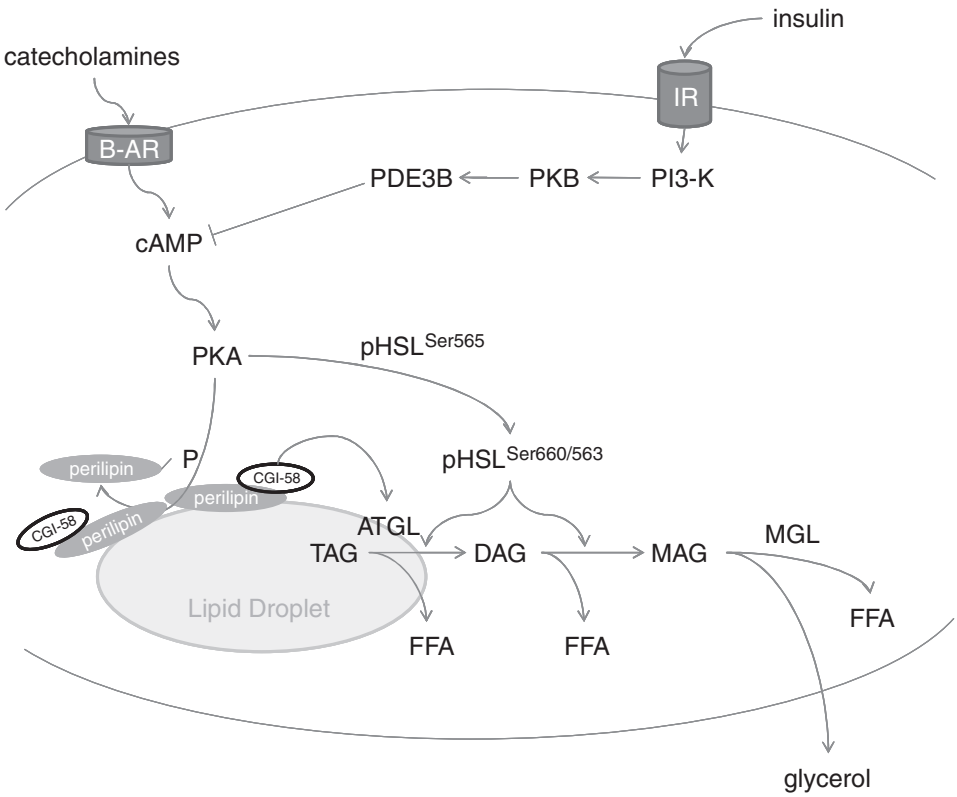

Fig. 2 – Regulators of lipolysis. There are many upstream regulators that function to stimulate or inhibit lipolysis by altering the activity of the lipase enzymes. Catecholamines stimulate lipolysis through cAMP- and PKA-dependent mechanisms. Protein kinase A activation results in the stimulatory phosphorylation of HSL on Ser^{660} and Ser^{563} and the dephosphorylation of inhibitory Ser^{565}. Protein kinase A also phosphorylates perilipins, further increasing HSL's lipolytic activity. Phosphorylation of perilipin also promotes the disassociation of comparative gene identification 58, allowing it to associate with ATGL and increase lipase activity. With elevated lipase activity, there is an increase in the breakdown of TAG and the release of glycerol and FAs. Insulin inhibits this lipolytic pathway by activating PDE3B, and thus hydrolyzing cAMP and reducing the activation of PKA.

levels. Cyclic AMP then activates protein kinase A (PKA), which phosphorylates downstream targets. Protein kinase A phosphorylates HSL on Ser^{660} and Ser^{563}, allowing it to translocate to the lipid droplet and initiate its lipase activity [16]. Protein kinase A also phosphorylates perilipin, a protein that is associated with the lipid droplet in the basal state and impedes lipase access and activity. The expression of perilipin protein is necessary to allow the translocation of HSL; and with phosphorylation of perilipin, HSL's lipolytic activity is enhanced [17]. It is also suspected that the phosphorylation of perilipin allows for the release of comparative gene identification 58, a protein that may then associate with ATGL and increase its lipolytic activity [18,19].

The β-adrenergic pathway can be inhibited by the breakdown of cAMP through phosphodiesterase (PDE) leading to a reduction in PKA activity. There are many isoforms of PDE, but PDE3B is the predominant isoform associated with lipolysis in adipocytes due to its high affinity for cAMP [20]. The antilipolytic hormone insulin is a main regulator of PDE3B and increases its activity via phosphorylation by protein kinase B (Akt), consequently reducing cAMP levels and thus lipolysis. These β-adrenergic effects on lipolysis occur quickly and allow for a large increase in lipolysis within seconds to minutes. The stimulatory effects of catecholamines are stronger in the visceral adipose tissue than in the subcutaneous tissue, likely because of enhanced functional α2-receptor activity in the later region [21]. There is evidence that GCs may be able to affect the β-adrenergic pathway as well, perhaps by altering cAMP levels [3,13,14,22]; however, their role is unclear, and there is much contradiction within the literature. A summary of GCs' effects on lipolysis and suggested mechanisms of action can be found in Table 1 and will be discussed further below. It is unclear whether effects on this pathway occur through a genomic mechanism, such as increased transcription of proteins, or through nongenomic effects that alter enzyme activity directly.

Several enzymes in the classic lipolytic pathway have been investigated to determine if GCs' effects on lipolysis occur through the β-adrenergic pathway. As the main regulator of β-adrenergic, stimulated lipolysis, cAMP is often the first target of investigation. Increases in cAMP levels with GC treatment would suggest a mechanism for increased lipolysis; however, few studies have seen this to be the case. Although there is evidence that GCs decrease protein kinase B and PDE expression and activity [23] and would thus be expected to cause increases in cAMP levels, such increases are not often found with GC treatment alone [9,24]. In one case, primary adipocytes treated with dexamethasone in vitro did produce an increase in cAMP levels [3]. These increases in cAMP concentrations were associated with decreases in PDE protein expression as well as increased PKA activity [3]. As would be expected with increases in PKA, these authors observed increased phosphorylation of HSL and perilipin. A surprising finding, however, was that this phosphorylation did not promote the translocation of HSL to the lipid droplet, as would be expected to occur with β-adrenergic agonists. Thus, the mechanisms of how GCs might stimulate the β-adrenergic pathways to promote lipolysis are still not clearly defined. In

Table 1 – Summary of previous studies investigating the effects of GCs on lipolysis

Article	Adipose model	Dose/type GC	Duration	Lipolysis	Suggested Mechanisms
Fain et al [50]	Isolated parametrial adipocytes; high-fat–fed rats	Dexamethasone 0.016 μg/mL (0.04 μmol/L)	4 h	↑ FFA release ↔ glycerol release	Altered transcription
Fain et al [9]	Isolated parametrial adipocytes; rat	Dexamethasone 0.1 μg/mL (2.5 μmol/L)	4 h	↔ Glycerol	↔ cAMP
Lamberts et al [24]	Isolated epididymal adipocytes; rat	Dexamethasone 0.1 μg/mL (2.5 μmol/L)	4 h	↔ Glycerol	↔ cAMP
Samra et al [76]	In vivo human	Hydrocortisone 1.5 μmol/L	Acute IV infusion	↑ Overall NEFA release ↓ NEFA venoarterial difference in abdominal	↑ LPL activity ↑ Peripheral lipase activity ↓ Visceral lipase activity
Ottosson et al [22]	Isolated subcutaneous abdominal adipocytes; human	Hydrocortisone 1 μmol/L	3 d	↓ Basal lipolysis ↓ β-Adrenergic–stimulated lipolysis	↓ Production or ↑ elimination of cAMP
Xu et al [3]	Isolated epididymal adipocytes; rat	Dexamethasone 0.1 μmol/L	24 h	↑ FFA release after 4 h ↑ Glycerol release after 16 h	↑ HSL and ATGL transcription ↓ PDE3B expression ↑ cAMP and PKA activity ↓ Perilipin expression ↑ Perilipin and HSL phosphorylation
Campbell et al [13]	3T3-L1 adipocytes	Corticosterone 1 μmol/L	48 h	↑ Glycerol release	↑ HSL and ATGL transcription
		100 μmol/L	48 h	↓ Glycerol release	↓ cAMP activity

NEFA indicate nonesterified fatty acid.

fact, recent evidence supports the notion that, at least in the short term, this pathway is downregulated by acute GC treatment, perhaps via nongenomic actions (see below).

4. Stress and excess adiposity link

Given that GCs are widely characterized as being "lipolytic" in action, it is odd that these hormones, when given exogenously or are elevated because of excessive endogenous production, are linked to increased adiposity. A recent meta-analysis of longitudinal studies has concluded that even perceived psychosocial stress, which increases GC secretion, is a significant, albeit small, risk factor for excess weight gain in humans [25]. The link between GCs and excess adiposity is well established clinically and is clearly demonstrated in individuals with Cushing syndrome [26] or those on exogenous corticosteroid treatment [27]. These individuals display increased weight gain, hypertension, and visceral adiposity and are at increased risk for developing type 2 diabetes mellitus [28]. Glucocorticoids appear to maintain their catabolic actions in other tissues causing reductions in bone mineral density and lean body mass, while increasing adipose mass and overall body mass in humans [29]. In rodents, the catabolic effects of GCs are more apparent than in humans, with significant reductions seen in body weight with the administration of GCs through corticosterone pellet implants [13] or via repeated dexamethasone injections [30]. However, there is some evidence that adipose mass is also increased relative to overall body mass in these animals [13,31], which suggests that GCs do have anabolic effects in the adipose tissue of rodents as in humans. Because GCs alter the release of several other hormones and adipokines [32,33] and influence both food intake and insulin sensitivity, it is not clear however if the adipogenic effects of GCs are direct or indirect in nature. Interestingly, adipose tissue–specific increases in GC action, via the upregulation of the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), also promotes increased visceral fat accumulation, thereby further suggesting that GCs may have a primary role in the development of central obesity [2,34] (see further discussion below). These anabolic effects likely result from a combination of factors including alterations to food intake as well as metabolic changes at the tissue level (topics that will be discussed in the sections below). Evidence points to GCs as the culprit of these anabolic effects, whereas catecholamines remain catabolic and lipolytic.

Glucocorticoids are not only released in the stressed state but are present at low levels in the basal (unstimulated) state as well. Basal GC release follows a diurnal rhythm in healthy humans, with elevated levels in the morning and low levels in the evening; this is the opposite in nocturnal rodents. These normal diurnal rhythms are important to regulate immune function, growth, metabolism, and behavior. Normal cortisol levels are between 5 and 15 μg/dL (~.15-.5 μmol/L) in the plasma of healthy patients [35], and healthy rodents have shown normal plasma corticosterone values that peak at around 300 ng/mL (~1 μmol/L) [13,36-39]. Although elevated GC levels seem to contribute to an increase in visceral adiposity, most obese individuals do not exhibit elevated peak plasma GC levels [40,41]. Interestingly, a combination of lower waking (peak) cortisol and higher evening (basal) cortisol in those with generalized or central obesity has recently been established [42]. These obese individuals also exhibit increased cortisol clearance and production rates [40] with increased HPA axis activation [43]. In line with this, obese Zucker diabetic fatty rats also have HPA hyperactivation, which occurs in association with increased visceral adipose tissue mass and the development of overt hyperglycemia [44].

Considerable evidence over the last 15 years suggests that GC levels within select tissue may by quite different than those circulating in the plasma [45]. When GCs are released, both active and inactive forms of the hormone are sent into circulation. Inactive GCs, cortisone in humans and 11-dehydrocorticosterone (11DHC) in rodents, travel freely in the plasma (ie, unbound to carrier proteins) in high levels; and the tissues possess varying levels of activating enzymes that are able to convert between the active and inactive forms. Two microsomal enzymes, collectively referred to as the *11β-hydroxysteroid dehydrogenase (11β-HSD) system*, interconvert receptor-active cortisol and inert cortisone (Fig. 3). Through intracellular cortisol amplification or inactivation, 11β-HSD represents an additional bidirectional regulatory step before active GCs binding to their intracellular receptors. 11β-Hydroxysteroid dehydrogenase type 1 is found predominantly in the liver, brain, skeletal muscle, and adipose tissue where it activates inactive cortisone and 11DHC. This amplifies the amount of active GCs in the given tissue and increases GCs' actions there. 11β-Hydroxysteroid dehydrogenase type 2 (11β-HSD2) is found predominantly in the kidney where it works to inactivate GCs, potentially acting as a protective mechanism to prevent tissue overexposure. Although it is difficult to adequately measure tissue levels of GCs, Masuzaki et al have suggested that adipose tissue may have GC levels that are 10 to 15 times those of circulating levels due to the actions of 11β-HSD1 [2].

Increasing levels of 11β-HSD1 that produce heightened GC levels in the adipose tissue are also linked to obesity. Elevated levels of 11β-HSD1 are found in the adipose depots of obese individuals [34,46]; and increasing 11β-HSD1 in a transgenic rodent model leads to increases in GC levels, increased food intake, and subsequent increases in adipose tissue mass [2]. It has also been reported that both 11β-HSD1 [47] and GR levels [2,48] are higher in visceral compared with subcutaneous adipose depots, with visceral adipocytes showing a greater ability to bind GCs [49]. This suggests that GCs have a larger impact in the visceral depot [47] and suggests reasons for the

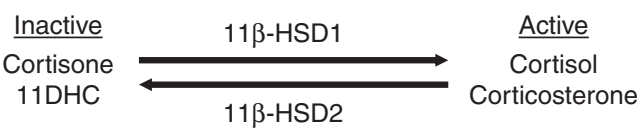

Fig. 3 – Actions of the 11ßHSD system. The 11ßHSD system allows for the conversion between active (cortisol in humans and corticosterone in rodents) and inactive (cortisone in humans and 11DHC in rodents) forms of GCs within the tissues.

site specific adiposity that results in individuals with elevated GC levels.

Although GCs have long been accepted as lipolytic hormones [3,9,14,15,24,50], clinical evidence clearly suggests that they can have a significant anabolic effect on fat deposition. Both catecholamines and GCs have the potential to affect behaviors, such as feeding, which could influence adipose accumulation, although GCs may also have more direct anabolic effects within adipose tissue to affect lipid metabolism. The following sections will discuss the various ways in which GCs may promote adipose accumulation.

4.1. *Stress hormones and food intake*

One way in which an increase in stress hormones and HPA activity could contribute to obesity is by influencing food intake. The catecholamines epinephrine and norepinephrine have been shown to increase feeding when injected into the brains of rodents [51]. The HPA activity and GC levels are linked to feeding as well, and the diurnal pattern can be altered in response to feeding times [52,53]. The HPA activity is increased in response to starvation or fasting [54], and GCs tend to increase feeding [55]. The elevation in GC levels may cause rodents [56] and humans [57] to choose high-caloric "comfort foods," a mechanism that seems logical in the case of starvation, as it would bring needed energy substrates into the body [52]. However, this may be maladaptive when GCs are elevated in the nonfasted state, such as the case of psychological stress. Individuals that respond to stressful events with high cortisol levels often choose to consume a greater number of calories; and these calories tend to come from high-fat, sweet foods [57]. Cushing disease patients also tend to pick high-fat products to eat compared with individuals without elevated GC levels [58].

Glucocorticoids may not affect appetite directly, but likely do so through influencing the levels of other hormones and neurotransmitters, such as neuropeptide Y (NPY) [57], proopiomelanocortin, and/or Agouti-related protein [59]. Neuropeptide Y is known to increase food intake as well as increase the proportion of energy that is stored as fat. Glucocorticoids are associated with an increase in NPY [55], which could explain the increased food intake. Individuals with Cushing syndrome are also found to have elevated levels of circulating triglycerides [28]; this may come as a result of increased fat intake and chylomicron circulation. It is possible, therefore, that stress hormones promote an increased caloric intake and thus produce a positive energy balance, along with increased circulation of FAs; and this together likely contributes to adipose accumulation.

4.2. *GCs and lipoprotein lipase activity*

In addition to increasing the availability of fatty acids through increased dietary intake of energy-dense, high-fat foods, GCs' effects on lipoprotein lipase (LPL) may further increase availability and uptake of FA into the adipose tissue. Triacylglycerol circulates in the blood as a component of either very low-density lipoproteins (VLDLs) or chylomicrons. Lipoprotein lipase is an enzyme that hydrolyzes the TAGs within these complexes and allows the release of FAs. Once released, the FAs can be taken up by the surrounding tissues for use or storage. In the fed state, LPL is increased in the adipose tissue to promote uptake and storage, whereas the opposite occurs in the fasted state [60]. An increase in LPL would be expected to increase FA uptake and storage in adipocytes. Glucocorticoids increase the activity of LPL either through increases in transcription or posttranslational modifications such as increased activation or decreased degradation [61-63]. Glucocorticoids may cause a greater increase in LPL activity in omental fat, particularly in men [64]. This would mean that a greater amount of FA would be available for uptake in the visceral region, and could help to explain the specific adipose accumulation seen in this depot in individuals with elevated GC levels. Catecholamines appear to work in an opposite fashion, maintaining their catabolic functions by causing decreased expression and activity of LPL [65].

4.3. *GCs and adipogenesis*

In addition to altering food intake and fatty acid availability, GCs can affect metabolism at the tissue level and promote the storage of these excess fatty acids. There are 2 ways through which adipose tissue mass may be increased in the development of obesity. Adipocytes may hypertrophy because of the increased synthesis and storage of lipids, or hyperplasia may occur because of increased differentiation of preadipocytes to mature adipocytes (ie, adipogenesis) [66]. Although both lipogenesis and adipogenesis may occur as a result of GC exposure, the later is a well-known effect. Adipose stromal cells, preadipocytes, are stimulated to differentiate into mature adipocytes by both cortisol and dexamethasone in a dose-dependent fashion [67]. In fact, it appears that GCs are required to induce the differentiation of both human adipose stromal cells as well as 3T3-L1 preadipocytes [67,68]. The presence of 11βHSD1 in the adipocytes, and thus an increase in tissue GC levels, also promotes the differentiation of adipose stromal cells to mature adipocytes [66], confirming GCs' adipogenic effects.

An increase in adipogenesis is a likely effect of GCs; however, if adipogenesis was the sole cause for adiposity, we would expect that individuals with elevated GC levels would have many small adipocytes. Evaluation of adipose morphology in Cushing patients shows that they have enlarged, hypertrophic adipocytes [1]; the same occurs in rodents treated with exogenous GCs [31]. Therefore, GCs must also stimulate hypertrophy, through either increased synthesis and storage or decreased breakdown, in addition to hyperplasia.

4.4. *GCs and lipid storage*

Adipose tissue is the main storage site for excess energy and lipids in the body, although deposition can be found in nonadipose sites (liver, muscle). Primarily, lipids stored in the adipose tissue come from FA and triglycerides that have been circulating in the blood either from dietary intake or secretion from the liver and have subsequently been hydrolyzed by LPL. As mentioned previously, GCs are known to increase dietary fat intake and upregulate LPL activity to increase the availability of FA. Glucocorticoids also appear to be able to promote increases in de novo lipogenesis, the

production of lipids from nonlipid substrates, such as glucose. Much attention has focused on the role of GCs on lipogenesis within the liver, and they appear to increase this process (reviewed by Berdanier [69]). Insulin is a known promoter of lipogenesis; and the synthetic GC, dexamethasone, has also been shown to potentiate these effects [70]. Increases in lipogenesis within the liver thus increase both storage within the liver and the secretion of VLDL [71]. Increased secretion of VLDL means that there is an increase in triglycerides in circulation to be taken up by the adipose tissue and a greater potential for lipid storage. Along with this, adipose tissue is able to undergo de novo lipogenesis itself. Little work has been done to investigate the effects of GCs on lipogenesis within the adipose tissue, however. Corticosterone, along with insulin, has been seen to increase lipid synthesis up to 66% in cultured adipose tissue [72]. However, other studies have reported marked decreases in fatty acid synthetase and acetyl CoA carboxylase, the rate-limiting enzymes of lipogenesis, in the adipose tissue of rats treated with GCs [73]. Further investigation of GCs' effects on lipogenesis within the adipose tissue is needed to determine how this may contribute to overall adipose accumulation.

Lipid storage may also be increased if liberated FAs are simply reesterified into triglycerides when elevations in GCs are present in the circulation. Evidence does not suggest that to be the case, however; and, in fact, GCs have been shown to reduce reesterification within adipose tissue. Jeanrenaud [74] concluded that the treatment of adipose tissue with GCs caused a decrease in FA reesterification, after observing a disproportionately high level of FA compared with glycerol in the media of adipocytes treated with dexamethasone. More recent work has supported this conclusion, finding that phosphoenolpyruvate carboxykinase expression is greatly reduced in the adipose tissue with GC treatment [75]. Phosphoenolpyruvate carboxykinase is an enzyme involved in glyceroneogenesis that is needed for reesterification to occur. If reesterification is reduced, lipid accumulation must occur because of increased storage of lipids delivered to the adipose tissue, lipogenesis, or decreases in lipolysis.

4.5. *GCs' antilipolytic effects*

As discussed previously, although the mechanisms of action remain unclear, there is considerable evidence to support the prolipolytic effect of GCs [3,13,24,38,50]. Adding to the uncertainty of lipolytic mechanisms is evidence that GCs may also have an antilipolytic role [13,22,76]. For example, treating 3T3-L1 adipocytes with corticosterone at levels that would be found in the plasma (<1 μmol/L) for 24 to 48 hours produces increases in lipolysis as previously demonstrated [13]; however, if corticosterone is removed from the media following incubation, lipolysis increases further during a 1-hour basal period (Fig. 4). If corticosterone concentrations are increased beyond 1 μmol/L to levels that may be present in the tissue because of the actions of 11β-HSD1, decreases in lipolysis are clearly observed even after 48 hours of treatment [13]. When these high doses of corticosterone are removed from the media, increases in lipolysis are observed, as was observed with the lower doses (Fig. 4). These results suggest that corticosterone is

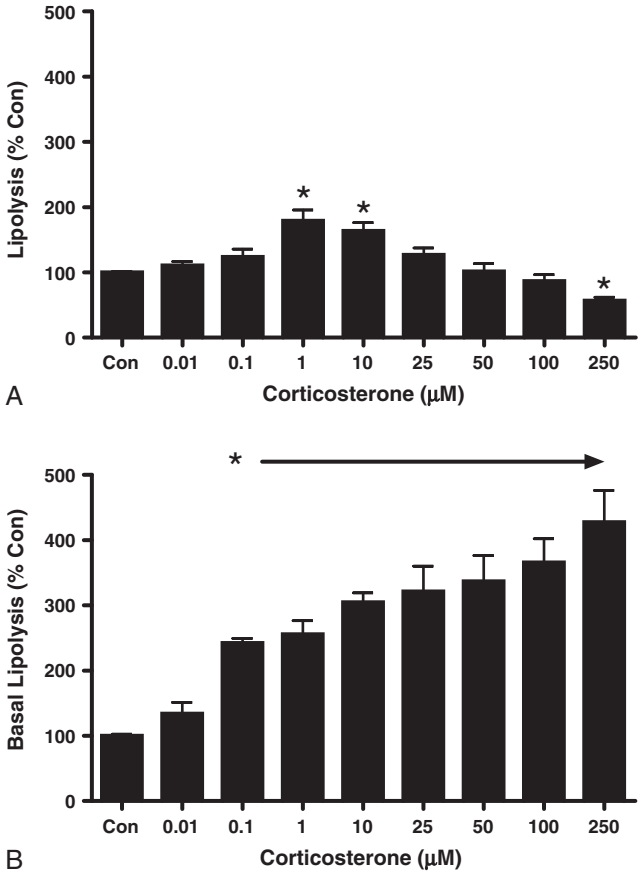

Fig. 4 – Lipolysis given 48 hours of corticosterone exposure and 1-hour basal lipolysis. Adapted from Campbell et al [13]. A, 3T3-L1 adipocytes were treated with corticosterone for 48 hours, and glycerol release was measured as a marker of lipolysis. Increases in lipolysis were seen with low doses of corticosterone (<25 μmol/L), whereas decreases in lipolysis were seen with higher doses (>25 μmol/L). B, Following the 48-hour exposure, corticosterone was removed from the media; and basal lipolysis was allowed to occur. Basal lipolysis was increased in all cells previously treated with corticosterone in a dose-dependent fashion, suggesting that there was an acute inhibitory effect when corticosterone was present.

able to upregulate expression of lipases and proteins along the lipolytic pathway, effects that remain after the removal of the hormone; however, while present, corticosterone may have acute inhibitory effects as well. Very little research has investigated this potential antilipolytic effect of GCs, but it is important when considering GC-induced adipose accumulation.

An in vivo study looking at FA efflux from subcutaneous abdominal adipose tissue also found decreases in lipolytic rate when subjects were given elevated levels of GCs compared with when they were given saline [76]. Total arterial levels of FA were increased with treatment; but the adipose venous FA levels were decreased compared with controls, suggesting decreased release from the abdominal tissue. These authors hypothesize that LPL activity and potential

increases in lipolysis in the peripheral tissue may account for the overall increase in FA while there are site-specific decreases in lipolysis in the abdominal region. It is also possible that site-specific increases in FA uptake are occurring; however, as suggested previously, it is believed that GCs reduce reesterification and thus would limit reuptake [74,75]. Similar decreases in lipolysis were also found when abdominal subcutaneous adipose tissue was cultured, treated with cortisol for 3 days, and then allowed to undergo basal or stimulated lipolysis [22]. It was speculated by the authors that GCs were able to either decrease the production or increase the elimination of cAMP to produce this response, although, unfortunately, measurements of cAMP levels were not conducted in that study. Decreases in lipolysis, particularly in specific adipose depots, may also contribute to excess adipose accumulation. Greater investigation is needed on this topic, however, because mechanisms of action are not clearly defined and it contradicts the traditionally accepted lipolytic role of GCs. Perhaps, with acute stress, these antilipolytic effects would be beneficial because they could counter the effects of catecholamines and prevent an excessive release of FA into circulation; however, when present in the long term, they may promote excessive adiposity.

5. Summary and future research directions

Acute increases in catecholamines and GCs during the fight-or-flight response have classically been proposed to allow the body to liberate stored energy substrates and meet the elevated metabolic needs of the body during the stressor. Although this is an adaptive and necessary response, chronic stress can be maladaptive and is linked to increases in obesity and metabolic disease. Research points to the long-term effects of elevated GC levels as the cause of this adipose accumulation. It appears that GCs may have this effect by acting on both the whole-body level as well as within the adipose tissue itself (Fig. 5). Glucocorticoids can affect the body as a whole to increase circulating fatty acids through an increase in dietary fat intake, increased lipogenesis and VLDL secretion from the liver, as well as increases in LPL activity. With a greater amount of FA in circulation, there is more to be taken up by the adipose tissue for storage. Furthermore, by increasing adipogenesis, there are a greater number of adipocytes in which these FA can be stored. Glucocorticoids also appear to have both lipolytic and antilipolytic effects within these adipocytes, depending on the dose and duration

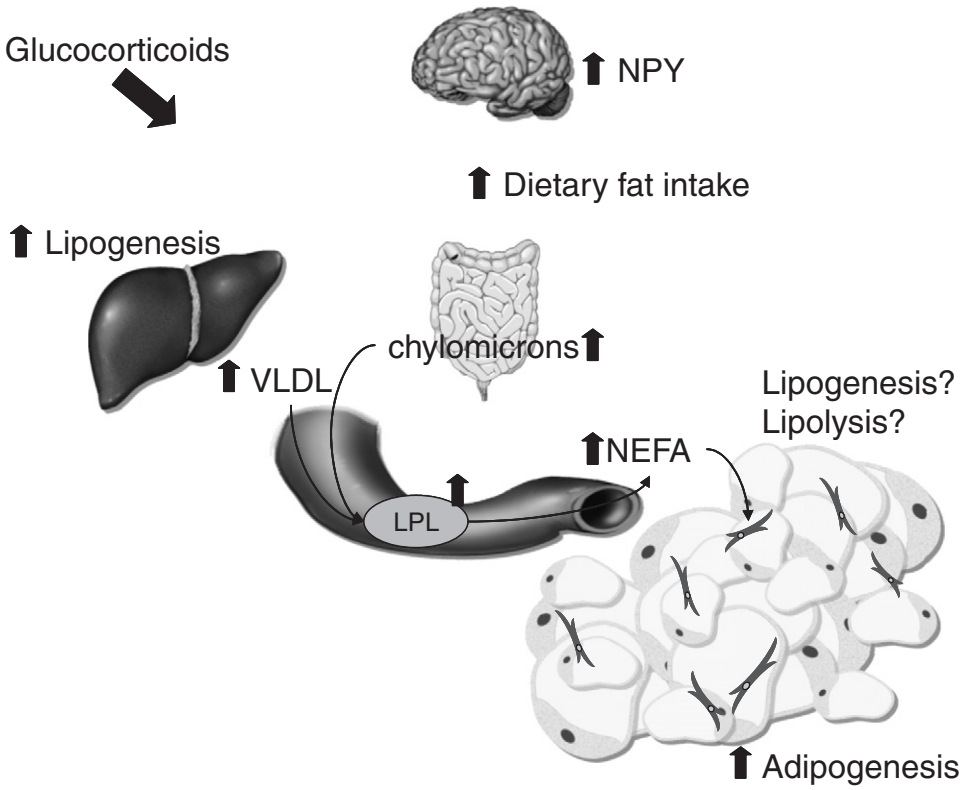

Fig. 5 – The overall effects of GCs on lipid accumulation. Glucocorticoids' diverse effects throughout the body contribute to the accumulation of lipids within the adipose tissue. Glucocorticoids increase NPY and stimulate an increase in food intake, particularly promoting increased intake of high-fat, sweet foods, resulting in elevated circulating chylomicron levels. Glucocorticoids also promote lipogenesis with the liver, resulting in increased VLDL secretion. Glucocorticoid-induced increases in LPL promote the hydrolysis of triglycerides stored within chylomicrons and VLDL, and result in the liberation of nonesterified FAs. These nonesterified FAs may then be taken up by the adipose tissue. Within the adipose tissue itself, GCs are known to promote adipogenesis; it is likely that increases in lipogenesis occur as well, although the effects on lipolysis remain unclear.

of exposure, although the mechanisms by which these metabolic effects occur are still unclear. Evidence from a number of studies suggests that GCs upregulate the expression of lipase enzymes, such as ATGL and HSL, through genomic effects to increase lipolysis, whereas more recent work also suggests that, when GCs are present in high amounts, they may inhibit lipolysis and increase lipid accumulation. Elevated levels and/or activation of GCs in the abdominal adipose tissue through elevated 11βHSD1 activity or GR expression may augment the antilipolytic effects of GCs and support lipid accumulation, as opposed to breakdown of triglycerides. It seems likely that both prolipolytic and antilipolytic mechanisms exist, but some may play larger roles than others depending on the adipose depot in question and the dose and duration of exposure. This would account for the diverse actions of GCs in the visceral and peripheral tissue, and explain the phenotype observed in individuals with elevated GC levels. Moreover, it may be that GCs have both genomic and nongenomic effects that cause differential acute and long-term results. Further investigation is thus required to determine how each of GCs' actions may occur in the different adipose depots and lead to adipose accumulation, as is frequently observed in persons who are on exogenous GC treatment or who suffer from high endogenous secretion of the hormone.

Funding

The works of authors discussed in this review were partially supported by the Natural Sciences and Engineering Research Council of Canada (grant 261306 to MC Riddell). AJ Peckett is a recipient of the Ontario Graduate Scholarship Program.

Conflict of Interest

None to declare.

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