MECHANISMS IN ENDOCRINOLOGY

Local and systemic effects of glucocorticoids on metabolism: new lessons from animal models

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Abstract

Glucocorticoids regulate a remarkable variety of essential functions, including development, immunomodulation, maintenance of circadian rhythm and the response to stress. Glucocorticoids acutely increase energy availability; this is accomplished not only by mobilizing energy stores but also by diverting energy away from anabolic processes in tissues such as skeletal muscle and bone. While this metabolic shift is advantageous in the short term, prolonged glucocorticoid exposure frequently results in central obesity, insulin resistance, hyperglycaemia, dyslipidaemia, muscle wasting and osteoporosis. Understanding how glucocorticoids affect nutrient partitioning is, therefore, critical for preventing the side effects of glucocorticoid treatment. Independently of circulating glucocorticoids, intracellular glucocorticoid activity is regulated by the 11 β -hydroxysteroid dehydrogenases 1 and 2 (HSD11B1 and 2), which activate and inactivate glucocorticoids, respectively. Excessive HSD11B1 activity and amplification of local glucocorticoid activity in tissues such as adipose tissue and bone may contribute to visceral obesity, insulin resistance and ageing-related bone loss in humans. Several recent findings in animals have considerably expanded our understanding of how glucocorticoids exert their dysmetabolic effects. In mice, disrupting glucocorticoid signalling in either adipose tissue or bone produces marked effects on energy homeostasis. Glucocorticoids have also been shown to influence brown adipose tissue thermogenesis (acute activation, chronic suppression), in both rodents and humans. Lastly, recent studies in mice have demonstrated that many dysmetabolic effects of glucocorticoids are sexually dimorphic, although corresponding results in humans are lacking. Together, these studies have illuminated mechanisms by which glucocorticoids exert their metabolic effects and have guided us towards more targeted future treatments for metabolic diseases.

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Invited Author's profile

Michael Swarbrick, PhD, is a Senior Hospital Scientist at the ANZAC Research Institute in Sydney, Australia. His first paper was published in *EJE* in 2001, and in the 20 years since, he has conducted research into obesity and its relationship with metabolic syndrome, using both humans and animal models. His postdoctoral work at the University of California, San Francisco, investigated monogenic causes of severe human obesity. This was followed by studies investigating the metabolic effects of adipocyte hormones, in response to nutritional and surgical interventions, with Prof. Peter Havel at the University of California, Davis. Since returning to Australia in 2008, Michael has investigated the beneficial effects of adipose tissue transplantation in mice, and he performed some of the first *in vitro* studies of human brown/beige adipocytes (with Dr Paul Lee). Michael is currently investigating the metabolic effects of glucocorticoids with Prof. Siebel and Zhou at the ANZAC Institute.

Introduction: glucocorticoids and metabolic disease

Glucocorticoids are steroid hormones required for normal development, immunomodulation, electrolyte balance and entrainment of the circadian rhythm. They are critical effectors of the physiological adaptation to stress, which affects each of these processes (1). Endogenous glucocorticoids (mainly cortisol in humans, corticosterone in mice) are secreted from the adrenal cortex. Excessive production of endogenous glucocorticoids, usually arising from a pituitary adenoma secreting adrenocorticotrophic hormone (ACTH), is the defining feature of Cushing's disease, a rare condition afflicting one to two patients/million/year. In contrast, exogenous glucocorticoids, such as dexamethasone and prednisone, are used therapeutically to suppress inflammation in autoimmune diseases. In Western countries, >1–2% of the population is currently being treated with glucocorticoids, with one-quarter of them taking it for five years or more (2).

Chronic exposure to glucocorticoids at high concentrations, regardless of their origin, produces characteristic changes in body composition (central obesity, sarcopenia, osteoporosis and skin atrophy) and metabolism (insulin resistance, dyslipidaemia, hypercoagulability and hypertension). Understanding how glucocorticoids produce these negative side effects is, therefore, critical for managing patients undergoing long-term glucocorticoid treatment.

The first purpose of this review is to outline the acute metabolic effects of glucocorticoids so that we can understand how chronic exposure contributes to metabolic and ageing-related diseases. During acute stress, glucocorticoids ensure survival by increasing energy availability for the brain, which relies on glucose for energy. This mobilization of energy stores diverts energy away from anabolic processes, such as bone formation or the maintenance of skeletal muscle mass. While this shift is advantageous in the short term, chronic glucocorticoid exposure predictably leads to the adverse effects listed above.

Glucocorticoid actions in target tissues depend not only on circulating concentrations but also on their intracellular availability. Thus, the local 'pre-receptor' availability of active glucocorticoids is regulated by 11 β -hydroxysteroid dehydrogenases 1 and 2 (HSD11B1 and 2), which activate and inactivate glucocorticoids, respectively (3). Excessive HSD11B1 activity, increasing local cortisol/corticosterone availability, is implicated in the aetiology of obesity and insulin resistance, as well as in ageing-related declines in cognition and lean mass.

These conditions represent an enormous and growing burden to societies worldwide; therefore, identifying the critical sites of glucocorticoid action is important for the future treatment and prevention of these diseases.

The second aim of this review is to highlight several recent findings in mice that have expanded our understanding of glucocorticoid actions in tissues that contribute to energy homeostasis. Specifically, disrupting glucocorticoid signalling in either adipose tissues (white and brown) or in bone has revealed that glucocorticoid actions in these tissues markedly influence body weight, adiposity and carbohydrate/lipid metabolism. In parallel, there is accumulating evidence that many dysmetabolic effects of glucocorticoids are sexually dimorphic, at least in mice. Together, these studies have considerably expanded our understanding of glucocorticoid physiology and have brought closer the possibility of tissue-specific glucocorticoid modulators for the treatment and prevention of metabolic disease.

The glucocorticoid system and its dysregulation in metabolic disease

There are many excellent reviews on glucocorticoid physiology in the literature (1, 4). Briefly, circulating glucocorticoids (cortisol/corticosterone) exhibit a diurnal rhythm, with peak levels at the time of arousal (morning in humans, evening in rodents) and higher levels during times of stress. In the circulation, glucocorticoids have short half-lives (~1 to 2 h for cortisol, 15–30 min for corticosterone (5)), and their bioavailability is limited by binding to corticosteroid-binding globulin (CBG/transcortin) (6).

Circulating glucocorticoids are regulated by the HPA (hypothalamic–pituitary–adrenal) axis (Fig. 1, left panel). Parvocellular neurons in the hypothalamic paraventricular nucleus (PVN) receive and integrate sensory inputs (related to nutrients, stressors, hormones and the time of day) from other CNS regions. These neurons activate the HPA axis by secreting appropriate amounts of corticotrophin-releasing factor (CRF) and arginine–vasopressin (AVP) into blood vessels leading to the anterior pituitary, which subsequently secretes ACTH into the circulation. ACTH then stimulates cortisol/corticosterone secretion from the adrenal cortex. When a fall in blood glucose concentrations is sensed, for example, this activates the HPA axis, triggering ACTH production and glucocorticoid release, which in turn stimulates hepatic gluconeogenesis. Further, HPA axis activation is prevented by the negative

Figure 1

Glucocorticoids acutely increase energy availability via coordinated actions in multiple metabolic tissues. Endogenous glucocorticoid concentrations are regulated by the hypothalamus–pituitary–adrenal (HPA) axis (left panel). In addition to following a pronounced diurnal rhythm, glucocorticoid secretion increases in response to diverse stimuli such as acute stress or declining blood glucose concentrations. At high circulating/tissue levels, glucocorticoids activate pathways in numerous tissues critical for systemic energy homeostasis, including the liver, skeletal muscle, white adipose tissue (WAT), brown adipose tissue (BAT) and pancreas. These actions are primarily directed at increasing systemic glucose availability. Reduced glucose utilization by osteoblasts in bone may indirectly contribute to increased systemic glucose availability. Mobilization of energy stores in this way ensures a steady supply of glucose to the brain during times of increased demand.

feedback actions of glucocorticoids upon CRF and ACTH secretion.

Glucocorticoids are ligands for two related nuclear receptors, the glucocorticoid receptor (GR, *NR3C1*) and the mineralocorticoid receptor (MR, *NR3C2*). GRs have a low affinity for cortisol and are widely distributed throughout the body, where they mediate glucocorticoid responses over a wide range of concentrations, such as during stress. In contrast, MRs bind both cortisol and mineralocorticoids (e.g. aldosterone) with high affinity, and their distribution is restricted to the renal tubule, sweat glands, colon and specific brain regions. MRs only respond to cortisol at low physiological concentrations, as they become saturated at higher concentrations. Following ligand binding, GRs and MRs undergo conformational changes and translocate to the nucleus, where they regulate the transcription of target genes (recently reviewed in (7)). It has been estimated that up to 20% of all genes respond to glucocorticoids (8).

Glucocorticoids also produce rapid non-genomic actions, which occur within minutes of agonist treatment and do not involve transcriptional regulation by GRs/MRs. In animal models, these actions include effects on

memory formation (9), negative feedback on the HPA axis (10) and inhibition of tracheal smooth muscle contraction (11). Interestingly, the rapid non-genomic responses to cortisol (and its inactive form, cortisone), as well as several synthetic glucocorticoids, involve the activation of the adhesion G-protein-coupled receptor G3/GPR97 (12), which is highly specific for human immune cells and is involved in antimicrobial responses (13).

As described above, intracellular activation/inactivation of glucocorticoids by HSD11Bs is also critical for their effects. HSD11B2 expression is restricted to the renal tubule, colon, sweat glands, placenta and developing brain, where it converts active cortisol (corticosterone in mice) to inactive cortisone (11-dihydrocortisone). In these tissues, HSD11B2 prevents inadvertent activation of the MR by cortisol, allowing aldosterone to bind instead (14, 15). In contrast, HSD11B1, which activates glucocorticoids, is much more widely expressed than HSD11B2, being particularly abundant in the liver, lungs, gonads, brain and adipose tissues. In these tissues, MR expression is much lower than that of GR (~250-fold lower in human adipocytes, for example (16)), and HSD11B's function is

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to amplify local glucocorticoid activity, independently of circulating cortisol concentrations.

Amplification of local glucocorticoid actions by HSD11B1 may contribute to central obesity and its associated metabolic complications. In human obesity, cortisol levels are not normally elevated (17), but increased adipose tissue HSD11B1 expression and/or activity has been reported in obese, insulin-resistant subjects compared to lean controls (18, 19), particularly in visceral adipose tissue (VAT) (20, 21). These differences have led many to hypothesize that high intracellular glucocorticoid availability in VAT contributes to central obesity and its metabolic sequelae in humans.

This concept is well supported by studies of HSD11B1-deficient mice, which are phenotypically indistinguishable from WT mice, although they do not develop stress-induced hyperglycaemia (22). When fed a high-fat diet (HFD), however, *Hsd11b1*^{-/-} mice gain less weight than WT mice and are protected against visceral obesity and glucose intolerance (23). Although HSD11B1 expression and activity are highest in the liver, studies in mice with a liver-specific knockout of HSD11B1 have revealed that HSD11B1 activity in extrahepatic tissues (i.e. adipose) makes a greater contribution to the deleterious metabolic effects of HFD feeding (24) or exogenous glucocorticoid excess (25).

Dysregulation of local glucocorticoids may also contribute to ageing-related declines in bone mass and cognition. Consistent with the deleterious effects of exogenous glucocorticoids on the bone (26), increased skeletal HSD11B1 expression and activity have been observed in both mice (27, 28) and humans (29) during ageing. In mice, chronic HFD feeding increases skeletal *Hsd11b1* mRNA expression, and the disruption of glucocorticoid signalling in osteoblasts and osteocytes (by transgenic overexpression of HSD11B2) protects against HFD-induced bone loss (30). Similarly, declining cognitive function with ageing in mice is also characterized by dysregulation of glucocorticoids in the hippocampus (31). Excessive glucocorticoid activity within tissues, independently of circulating glucocorticoids, has been proposed as a common underlying cause of metabolic and ageing-related diseases and has led to the development of HSD11B1 inhibitors for these conditions (32).

Glucocorticoids acutely increase nutrient availability

The acute effects of glucocorticoids on energy homeostasis are complex but can be broadly summarized

as the mobilization of energy stores (Fig. 1), to ensure a continuous supply of glucose to the brain. This shift also diverts energy away from anabolic processes such as bone formation or the maintenance of muscle mass, which are not immediately necessary for survival. Insulin is normally secreted in response to feeding, increasing glucose utilization by stimulating glucose uptake and glycolysis in tissues, while concomitantly suppressing gluconeogenesis. Acute glucocorticoid effects involve both synergy with and antagonism of insulin's actions, depending on the tissue or fed/fasted state, as well as interactions with catecholamines, which are secreted immediately in response to stress (1). While the metabolic effects of glucocorticoids have been well-studied in humans, here, we will use results from studies in rodents and cell lines to illustrate the underlying mechanisms.

In humans, acute glucocorticoid-induced increases in glucose availability are achieved by suppression of glucose-stimulated insulin secretion (GSIS) (33), insulin secretory tone (34) and by inhibition of hepatic insulin action (35). Studies in rat insulinoma cell lines suggest that glucocorticoids may further impair insulin secretion by inducing apoptosis in pancreatic β -cells (36, 37). In the liver, glucocorticoids suppress insulin action both directly (they stimulate transcription of the gluconeogenic enzymes phosphoenolpyruvate carboxykinase (PEPCK) (38) and glucose-6-phosphatase (G6PC) (39) in rat hepatoma cells) and also indirectly via sympathetic projections from the hypothalamic arcuate nucleus (ARC) to the liver, as shown in rats (40). Rodent studies indicate that glucocorticoids also stimulate hepatic glycogen production (41).

Increased glucose availability in glucocorticoid-treated humans is also facilitated by reduced whole-body glucose clearance (42). In stressed human patients suffering from trauma or from severe burns, for example, the maximal glucose uptake rate in peripheral tissues was reduced by ~35% compared to controls (43). Mechanistic studies in rats have shown that glucocorticoids acutely inhibit glucose uptake into skeletal muscle by preventing insulin-stimulated translocation of SLC2A4 (GLUT4) to the plasma membrane (44) and also increase muscle breakdown (proteolysis) by inducing the ubiquitin ligases TRIM63 (MuRF1) and FBXO32 (MAFbx) (45).

In the fed state, glucocorticoids synergize with insulin to stimulate lipogenesis (5), as demonstrated in cultured human adipocytes (46). Glucocorticoids stimulate lipogenic genes, such as fatty acid synthase (*FASN*) and acetyl-CoA-carboxylase (*ACACB*) (46) and also increase

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hepatic expression of the fatty acid scavenger receptor CD36 (47). In the absence of insulin (fasting), however, glucocorticoids inhibit lipogenesis in cultured human adipocytes (46), and systemic lipid availability is increased via angiopoietin-like 4 (ANGPTL4) secretion from adipose tissue and liver (48). ANGPTL4 increases fatty acid availability in two ways: (i) by promoting lipolysis (hydrolysis of stored triglycerides into non-esterified free fatty acids (NEFA) and glycerol) in adipose tissue; and (ii) also by inhibiting lipoprotein lipase (LPL) (48), the enzyme primarily responsible for the hydrolysis of chylomicrons and VLDL-triglycerides (and fatty acid uptake) in adipose tissue and skeletal muscle. In this manner, glucocorticoids increase energy availability in the fasting state (Fig. 1).

In adipose tissue, glucocorticoids antagonize insulin's anti-lipolytic actions, although these effects are less than seen in other tissues, such as skeletal muscle (49, 50). Dexamethasone increases lipolysis in 3T3-L1 adipocytes, by inhibiting the expression of *Plin1* (perilipin 1, which protects lipid droplets from hydrolysis), and concomitantly by increasing the expression of *Pnpla2* (known in humans as adipose triglyceride lipase, ATGL) (51). Together with the increased amounts of specific amino acids obtained from muscle breakdown, the increased glycerol and NEFA from lipolysis provide the necessary precursors and energy to drive hepatic gluconeogenesis. Interestingly, glucocorticoid-induced increases in gluconeogenesis, proteolysis and lipolysis can occur in the absence of insulin, as they are preserved in animal models of streptozotocin-induced (insulin-deficient) diabetes (52).

Glucocorticoids also increase systemic energy availability by inhibiting anabolic processes in bone. Exposing human osteoblasts (responsible for bone formation) to dexamethasone induces genes related to apoptosis and oxidative stress (53); and in humans, i.v. glucocorticoids treatment leads to a rapid (within 24 h) fall in the bone formation markers, osteocalcin (54) and P1NP (55). Acutely, sympathetic nervous system activity inhibits bone formation as osteoblasts and osteocytes express β_2 adrenergic receptors (56) and mice lacking catecholamines have increased bone formation (57).

The acute energy-sparing effects of glucocorticoids do not apply to brown adipose tissue (BAT), however. BAT is a specialized thermogenic organ that is activated by the sympathetic nervous system, and it uses circulating glucose and NEFAs to generate heat in response to feeding or cold exposure (diet- and cold-induced thermogenesis, respectively). While BAT is abundant in rodents and young mammals, small quantities have been recently rediscovered in human adults, prompting

its re-evaluation as a therapeutic target for obesity and type 2 diabetes (58). In humans, glucocorticoids acutely increase BAT activity (59) by stimulating cold-induced glucose uptake into BAT and by directly increasing cellular respiration in isolated human brown adipocytes (60). It is possible that acute glucocorticoid-mediated BAT activation is directed at counteracting the increased availability of glucose and NEFAs. In the long-term, however, chronic glucocorticoid treatment suppresses BAT activity (see below).

Chronic metabolic effects of glucocorticoids

While the mobilization of energy stores by glucocorticoids is undoubtedly beneficial during stress, maintaining this response over the long term produces undesirable effects on health. In cases of chronic glucocorticoid exposure (whether due to Cushing's disease or exogenous glucocorticoid treatment), continually increased substrate availability and inhibition of anabolic processes promote hyperglycaemia, dyslipidaemia, fatty liver, hepatic and peripheral insulin resistance, muscle atrophy, immunodeficiency, growth retardation, osteoporosis, topical skin thinning, glaucoma, infertility, depression and anxiety (Fig. 2). These metabolic effects are serious, as untreated Cushing's disease has a 5-year mortality rate of ~50% (61).

Chronic glucocorticoids and obesity

Weight gain, due to increased appetite (62) rather than suppression of resting energy expenditure (60, 63), is one of the most significant side effects of chronic glucocorticoid treatment. In humans treated with exogenous glucocorticoids, weight gain is common but highly variable: ~10% of subjects gain >10% of their body weight, although many (45%) experience no weight change at all (64). Interestingly, glucocorticoids may also affect macronutrient preference, as healthy women who increased their cortisol levels upon stress exposure also increased their intake of sweets and high-fat foods (65). The stimulatory effects of oral glucocorticoids on appetite and weight gain have led to reduced patient compliance, particularly among young women (66).

The influence of glucocorticoids on weight gain was first established in studies of mice with severe hyperphagic obesity (due to defective leptin signalling); these mice also exhibited adrenal hyperplasia and high corticosterone levels, and weight gain was prevented by

ACUTE glucocorticoid effects**CHRONIC glucocorticoid effects** **Figure 2**

Chronic glucocorticoid excess promotes obesity, insulin resistance and dyslipidaemia via their effects on multiple metabolic tissues. Many of the dysmetabolic side effects of glucocorticoid exposure result directly from their acute effects to mobilize energy stores (see text). Chronically, however, the stimulatory effects of glucocorticoids on hepatic gluconeogenesis and lipogenesis lead to insulin resistance and steatosis, respectively. This is likely exacerbated by impaired hepatic insulin clearance. The increased secretion of TG-rich VLDL particles from the liver leads to dyslipidaemia and results in lipid accumulation in skeletal muscle and adipose tissues. Chronic glucocorticoid exposure also promotes insulin resistance in adipose tissue and skeletal muscle, further reducing glucose uptake by these tissues. Glucocorticoid-mediated suppression of anabolic processes in skeletal muscle and bone leads to muscle atrophy and osteoporosis, respectively. Visceral adipose tissue (VAT) is a particularly important site of action for glucocorticoids, due to the amplification of glucocorticoid actions by 11β-HSD1 in this depot and its close relationship with dyslipidaemia and hepatic insulin resistance (see text).

adrenalectomy (67). Similarly, in mice with diet-induced obesity, treatment with either the GR antagonist CORT 108297 or mifepristone (a GR and progesterone receptor antagonist) prevented weight gain (68).

GRs are widely expressed in the CNS, particularly in the hippocampus and in hypothalamic nuclei involved in feeding, including the ARC, parvocellular neurons of the PVN and the ventromedial hypothalamus (69). In cultures of ARC-derived hypothalamic neurons, dexamethasone increased mRNA expression of genes encoding the orexigenic peptides neuropeptide Y (*Npy*) and agouti-related protein (*Agrp*) (70).

Glucocorticoid-induced hyperinsulinaemia may further exacerbate weight gain. Although glucocorticoids

acutely suppress GSIS in humans (see above), insulin resistance resulting from chronic glucocorticoid exposure provokes compensatory increases in insulinaemia and GSIS (71) (Fig. 2). Fasting hyperinsulinaemia is a strong predictor of future weight gain in human adolescents (72). Although there are no data from humans at present, rodent studies suggest that this situation is further exacerbated by impaired insulin clearance: 5 days of dexamethasone treatment impaired the activity of the hepatic insulin-degrading enzyme (IDE) in rats and mice (73). Chronic hyperinsulinaemia can itself promote obesity, as mice lacking one of their two insulin genes and fed a HFD have lower insulin levels and are protected against weight gain, compared to WT mice (74).

Effects of glucocorticoids on adipocytes and adipose tissue

Glucocorticoid excess also has direct effects on adipocytes and adipose tissue, including increased adipocyte size (hypertrophy), increased adipocyte number (hyperplasia) and altered secretion of adipose-derived hormones (adipokines). Microarray studies of human adipose tissue indicate that glucocorticoids promote lipid *turnover*, which involves increases in both lipid synthesis and breakdown (75). The metabolic response to glucocorticoids in adipose tissues is heterogeneous, however, as chronic glucocorticoid exposure leads to preferential expansion of central depots (VAT), at the expense of s.c. adipose tissue (SAT).

Adipose tissue distribution is a critical determinant of susceptibility to metabolic syndrome, a phenotypic cluster in insulin-resistant humans consisting of central obesity, glucose intolerance, hypertension and dyslipidaemia (76). The metabolic syndrome markedly increases the risk of both cardiovascular disease and type 2 diabetes (77). Accumulation of VAT (strictly defined as fat residing inside the abdominal cavity and drained by the portal circulation, for example, omental, mesenteric, retroperitoneal) is metabolically unfavourable due to its relationship with insulin resistance and cardiovascular disease (78). VAT generally has a higher rate of lipid turnover than SAT, as it has higher levels of LPL activity (79) (giving it a greater capacity for binding and internalizing circulating triglycerides) and a higher sensitivity to lipolytic stimuli (in men, although the opposite relationship is observed in premenopausal women) (80).

Adipocyte hypertrophy in VAT contributes to insulin resistance in three main ways: (i) promoting hepatic NEFA flux and ectopic lipid deposition (81); (ii) increased macrophage infiltration and inflammation in VAT (82); and (iii) an altered pattern of adipokine secretion (83). In contrast, SAT, particularly in the gluteofemoral depot, has a lower lipolytic rate and protects against metabolic syndrome (84).

VAT is an important site of glucocorticoid action. First, VAT possesses more receptors for glucocorticoids than SAT (85). Microarray studies support heightened responsiveness of carbohydrate and lipid metabolic pathways to glucocorticoids (75), and greater glucocorticoid-induced insulin resistance (86) in human omental vs s.c. fat. The greater induction of insulin resistance by glucocorticoids in VAT, compared to SAT, is supported by results from human studies *in vivo* as well as primary adipocyte cultures from these depots (49).

Secondly, enhanced glucocorticoid responsiveness in VAT also reflects the increased expression and/or activity of HSD11B1 in this depot (18-21). Preferential energy storage in VAT, where it is more easily mobilized, suggests that glucocorticoids may recruit this depot in anticipation of future stressors, described as a 'preparative' effect (1).

Adipose tissue HSD11B1 activity has been linked with metabolic syndrome in rodent studies. Transgenic mice overexpressing HSD11B1 in adipose tissue, under the control of the aP2 promoter, developed greater central obesity and insulin resistance on a HFD than equivalent WT mice (87). Conversely, overexpression of HSD11B2 (which inactivates glucocorticoids) in the same tissues conferred a degree of protection against HFD-induced obesity, glucose intolerance and insulin resistance in follow-up studies (88). One important caveat of these studies is that the aP2 promoter is not adipocyte-specific; being also expressed in the brain, endothelial cells, macrophages, adipocyte precursors, cardiomyocytes and embryonic tissues (89). Regardless, a study of rats fed with high-sucrose/high-fat diet and treated with an HSD11B1 inhibitor also suggested that certain VAT depots may be critical sites of HSD11B1 activity. HSD11B1 inhibitor treatment not only reduced liver fat and circulating triglycerides but also reduced adipocyte size and lipogenic gene expression, while increasing those involved in lipid oxidation, specifically in mesenteric fat (90). These effects were not observed in epididymal or retroperitoneal fat.

Historically, studies using preadipocyte cultures suggested that the adipogenic effects of glucocorticoids may promote obesity via adipocyte hyperplasia (91). Elegant studies, more than 25 years ago, identified a transcription factor 'cascade' regulating adipogenesis, involving the transcription factors CEBPA (C/EBP α), CEBPB (C/EBP β) and CEBPD (C/EBP δ), and PPARG, irreversibly driving the development of fat cells by inducing each other's expression (91, 92). CEBPB and CEBPD are expressed very early in adipocyte differentiation, while CEBPA is induced by both CEBPB and CEBPD, whereupon it controls the acquisition of the mature adipocyte phenotype (91). Glucocorticoids (and the activated GR) contribute to this adipogenic programme by rapidly inducing CEBPD expression (91, 93) and by associating with CEBPB to activate PPARG, the master regulator of adipogenesis (94). Glucocorticoids also induce the adipogenic transcription factor KLF15, which also activates PPARG (95).

In recent years, however, the requirement for glucocorticoids in adipogenesis has been challenged. In 3T3-L1 cells, adipogenesis is impaired by knockdown of GR, due to impaired PPARG activation (94). Similarly,

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adipocyte precursors lacking GR have an impaired ability to undergo adipogenesis (96, 97), although they do catch up to WT cells later (96). Interestingly, implanting GR-deficient preadipocytes into male mice yielded small fat pads that were fully formed, even in adrenalectomized mice, suggesting that glucocorticoids and the GR enhance adipogenesis but are not essential for adipose tissue development (97).

Glucocorticoid actions in fat have also been investigated using adipose-specific GR knockout (AGRKO) mice, using adiponectin-Cre, which is specific for mature adipocytes (89). Compared to WT mice, AGRKO mice are indistinguishable from their WT littermates with respect to body weight, body composition and adipose tissue morphology (51, 98). Metabolic studies in AGRKO mice indicate that although glucocorticoids are dispensable for adipocyte development, they are critical for the regulation of lipolysis. Deleting GR from adipose tissues reduces lipid efflux to the liver during fasting, and AGRKO mice are protected against weight gain and hepatic steatosis in old age (98).

Lastly, glucocorticoids also influence the synthesis and secretion of adipokines, which often have systemic effects on energy homeostasis and insulin sensitivity. Dexamethasone directly stimulates transcription of the leptin (*ob*) gene in adipose tissue (99). Leptin levels in Cushing's patients are higher than in subjects matched for adiposity, and they decline following surgical treatment, before weight loss (100). Glucocorticoids also inhibit the synthesis and secretion of adiponectin, the insulin-sensitising adipokine (101), although adiponectin concentrations are not dysregulated in Cushing's patients (102). Regardless, it is more likely that the effects of glucocorticoids on central obesity and insulin resistance result from dysregulation of appetite and lipid flux than changes in adipocyte-derived hormones *per se*.

Glucocorticoids and BAT thermogenesis

As described earlier, glucocorticoids exert biphasic effects on BAT function: acutely, they stimulate cold-induced BAT thermogenesis (60), while BAT activity is suppressed by chronic glucocorticoid treatment. BAT thermogenesis is regulated by uncoupling protein-1 (UCP1), a mitochondrial membrane protein that generates heat by uncoupling substrate oxidation from ATP production (103). Studies in obese Zucker rats (lacking functional leptin receptors) suggested that defects in BAT thermogenesis and UCP1 activity were glucocorticoid-dependent, as they were resolved by adrenalectomy

(104). In healthy rats, corticosterone treatment dose-dependently inhibits UCP1 activity and thermogenesis (105); and in cultured human brown adipocytes, similarly, dexamethasone inhibits adrenergically-stimulated respiration (106). Interestingly, the suppressive effects of glucocorticoids on BAT are enhanced by induction of HSD11B1 expression and activity in this tissue (107). As for adipogenesis, glucocorticoids (and the GR) are not essential for brown adipocyte development (96), thermogenic gene expression, or the response to cold exposure (108), although they do exert some influence on these processes, likely aimed at conserving energy during chronic stress.

Intracellular lipid accumulation ('whitening') is a striking feature of glucocorticoid-treated BAT in rodents (105), that is also resolved by adrenalectomy (109). In mice treated with corticosterone for 4 weeks, we observed marked lipid accumulation in BAT, together with an ~8% decrease in UCP1 protein expression (110). Elsewhere, treating mice with the GR antagonist CORT125281 increased both fatty acid uptake and combustion in BAT (111). The factors contributing to BAT whitening are not well understood: we could not attribute it to changes in adipogenic (*Pparg*) or lipogenic (*Acaca*, *Fasn*) gene expression (110).

Intriguingly, two recent studies in mice implanted with corticosterone pellets have independently concluded that glucocorticoids stimulate BAT whitening by disrupting circadian rhythms related to lipid uptake (112, 113). The uptake of triglyceride-derived fatty acids into BAT displays a circadian rhythm in mice: it is highest in the evening (when endogenous glucocorticoids are elevated), and this pattern was disrupted within a few days of pellet implantation (112, 113). Lipid uptake was not perturbed by daily injections of corticosterone in the evening, however, suggesting that continuous elevation of corticosterone levels is required for BAT whitening. Interestingly, human BAT also displays a diurnal uptake of glucose (114) and lipids (115) from the circulation, although peak uptake occurs in the morning instead.

Transcriptomic analysis of BAT from corticosterone-treated mice revealed increases in genes involved in lipid synthesis and degradation, including *Lpin1* (encoding lipin-1, which regulates adipose tissue triglyceride metabolism) and *Acsf5* (Acyl-CoA synthetase medium chain family member 5). Corticosterone-mediated flattening of circadian rhythm also induced expression of the lipid uptake receptor CD36, and corticosterone-induced obesity and lipid accumulation in BAT and VAT were partially abrogated in CD36-null mice (113).

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These studies have illuminated potential relationships for further study in humans, linking chronic stress and/or disruption of a circadian rhythm with blunted BAT activity and dysregulated lipid metabolism.

Chronic glucocorticoids and bone

Consistent with its suppression of anabolic processes, chronic glucocorticoid treatment, even small doses, can dose-dependently cause bone loss and increase fracture risk in human adults (26). Studies in mice have shown that glucocorticoids promote apoptosis in osteoblasts (116) while favouring the development of adipocytes over osteoblasts in common bone marrow precursors (117). At the same time, glucocorticoids increase the survival of bone-resorbing osteoclasts (118), resulting in excessive bone resorption relative to formation. Glucocorticoid-induced bone loss occurs rapidly, within a few days of exposure, as shown in a sheep model of burn injury (119).

We and others have found that disrupting skeletal glucocorticoid signalling, by transgenically overexpressing 11 β -HSD2 in osteoblastic cells (osteoblasts and osteocytes), protects against bone loss induced by chronic stress (120), HFD (30) and ageing (27). Interestingly, disrupting glucocorticoid signalling in these cells also produced beneficial metabolic effects. Unlike WT mice, transgenic HSD2^{OB/OCY}-tg mice were protected against ageing-related declines in leptin sensitivity: as they aged, HSD2^{OB/OCY}-tg mice maintained their leptin-mediated suppression of food intake and stimulation of adipose tissue sympathetic outflow, in contrast to their WT littermates (121). While the mechanisms linking osteoblastic glucocorticoid signalling with the CNS are not well understood, they do not appear to involve changes in the osteoblast-derived hormones osteocalcin or lipocalin-2 (121). Similarly, deleting the GR from osteoprogenitor cells also reduces body weight in mice by ~10% (122).

Notably, when HSD2^{OB/OCY}-tg mice were fed HFD, they not only increased their rates of bone formation and skeletal glucose uptake compared to WT mice but they were also protected against HFD-induced central obesity, insulin resistance, glucose intolerance and dyslipidaemia (30). It is, therefore, conceivable that during stress, glucocorticoids limit energy (glucose) uptake into osteoblasts and osteocytes, which is used by these cells for anabolic processes (bone formation and remodelling, respectively). Other studies in mice have shown that increasing the uptake and utilization of glucose by these cells produces marked beneficial effects on whole-body glucose homeostasis (123). Further studies will be

required to confirm whether glucocorticoid signalling in osteoblasts and osteocytes makes a similar contribution to whole-body metabolism in humans.

Sexual dimorphism in glucocorticoid action

Glucocorticoid-regulated metabolic pathways display a marked sexual dimorphism in humans. For example, women have a greater predisposition to inflammatory diseases (124); and during fasting, women (but not men) synthesize lipids from amino acids (125). In addition, men commonly possess an android pattern of fat distribution, with more VAT and less gluteofemoral SAT than women, and women are generally protected from the cardiometabolic consequences of obesity, at least until after menopause (126). Similarly, male rodents are preferred for metabolic studies as they are more sensitive to HFD (127).

Pioneering studies on the sexually dimorphic effects of glucocorticoids were performed by Cidlowski's group, who showed differential induction of hepatic gene expression by glucocorticoids between male and female rats, with a greater anti-inflammatory response in males (128). Further studies in mice confirmed that nearly one-quarter of inflammatory genes in the livers were sexually dimorphic. Differentially regulated pathways were related to bacterial/viral recognition, rheumatoid arthritis, the complement system, and TREM1 and NF κ B signalling (129). Functionally, female mice displayed an exaggerated IL1B response to lipopolysaccharide injection compared to males.

Many other metabolic effects of glucocorticoids have been found to be sexually dimorphic. Male mice are more sensitive to the dysmetabolic effects of chronic glucocorticoid excess (central obesity, hyperinsulinaemia, hyperglycaemia, dyslipidaemia and BAT whitening) than females (110, 130), independently of the dose, duration or route of administration (drinking water vs pellet). Interestingly, corticosterone-induced loss of lean mass was equivalent between males and females, suggesting that this response is not sex-dependent (110). The lack of sexual dimorphism in skeletal muscle glucocorticoid responses has been described in microarray studies (131).

The increased sensitivity of males to glucocorticoids likely reflects differences in both HPA axis regulation and in tissue-specific glucocorticoid actions. Differences in the HPA response to restraint stress have been reported between male and female mice (132). In addition, CBG/transcortin levels are usually higher in female mice;

Figure 3

Androgens and oestrogens exert both synergistic and antagonistic effects on glucocorticoid actions, and these effects are tissue-specific. Glucocorticoid-regulated metabolic pathways display a marked sexual dimorphism in mice. Compared to females, male mice have a more exaggerated hepatic inflammatory response to infection and are more susceptible to glucocorticoid-induced obesity, insulin resistance and dyslipidaemia. Recent studies have indicated that androgens exacerbate many of the dysmetabolic effects of chronic glucocorticoid exposure. Ectopic lipid accumulation in highly metabolically active tissues, such as skeletal muscle and BAT, interferes with insulin action and results from increased hepatic VLDL-TG export. In parallel, studies in mice have shown that oestrogens antagonize many of the dysmetabolic effects of glucocorticoid treatment, and may, in part, explain the protection from cardiovascular disease in premenopausal women. In mice, oestradiol protects against diet-induced obesity and insulin resistance, while the metabolic effects of chronic glucocorticoid exposure become more apparent following ovariectomy.

therefore, there may be more active glucocorticoids circulating in males (133). In rat livers, HSD11B1 activity and expression are also generally higher in males than in females, and it is suppressed by oestradiol (134).

Indeed, oestrogens antagonize many metabolic effects of glucocorticoids (Fig. 3). Oestrogen suppresses the number of corticosteroid-binding sites in the pituitary (135), and central oestradiol infusion increases leptin's anorexic effects in rats (136). In breast cancer cells, oestrogen inhibits GR function by reducing its ligand-mediated phosphorylation and activation of target genes (137). During pregnancy, increases in circulating oestrogen (from the placenta) also stimulate hepatic production of CBG/transcortin, which, in turn, reduces

both the levels of free cortisol and its negative feedback on the HPA axis (138). Accordingly, treating male mice with oestradiol prevented diet-induced obesity, hyperinsulinaemia and glucose intolerance (139), and some dysmetabolic effects of corticosterone treatment (obesity and hypercholesterolemia) only became evident in female mice after ovariectomy (110). Ovarian hormones prevent activation of hepatic glucocorticoid signalling, which manifests as steatosis and insulin resistance in ovariectomized mice (140).

In parallel, androgens have been found to potentiate glucocorticoid-induced dysmetabolism in mice. Spaanderman *et al.* reported that co-administration of an androgen receptor (AR) agonist in male mice potentiated

the effects of corticosterone on GR target genes in WAT (and to some extent, BAT) (141). These effects were abolished by treatment with the AR antagonist enzalutamide. While the underlying mechanisms are incompletely understood, in this model, enzalutamide inhibited corticosterone-mediated induction of HSD11B1 activity in WAT. Similarly, treating female rats with 5 α -dihydrotestosterone increased hepatic HSD11B1 expression and GR activity (142). We have also found that many of the dysmetabolic effects of chronic corticosterone exposure (hyperinsulinaemia, insulin resistance, dyslipidaemia and BAT whitening) in mice were androgen-dependent (110). Notably, in other tissues, such as skeletal muscle, androgens can antagonize glucocorticoid actions (143).

The underlying mechanisms are complex but may include reciprocal regulation of target genes by AR and GR, as has been shown in some castration-resistant prostate cancers (144). Reciprocity between AR and GR may explain, at least in part, why adipogenesis is impaired in preadipocytes lacking GR *in vitro*, but their implantation into male mice yields fully formed fat pads (97). AR and GR share many genomic binding sites, but AR/GR specificity depends on many other factors, including the DNA sequence of the response element, nearby enhancers, chromatin accessibility (145) and potentially by the expression of co-factors such as *Bag1* and *Ppid* (146).

This situation is further complicated by glucocorticoid-induced GR resistance: for example, leukocytes from Cushing's patients exhibit subtle changes in the distribution of GR splice variants that reduce dexamethasone binding (147). Regardless of the exact mechanism, there is substantial emerging evidence that many of the dysmetabolic effects of glucocorticoids are androgen-dependent. This idea raises many exciting possibilities for the future treatment of metabolic diseases in humans, particularly for women with polycystic ovary syndrome (which is characterized by androgen excess) and clinical features of the metabolic syndrome (148).

Conclusions

By regulating systemic nutrient availability, glucocorticoids are critical for many essential physiological functions, most notably the response to stress (1). Chronic exposure to (endogenous/exogenous) glucocorticoids not only suppresses inflammation and mobilizes energy but also promotes muscle loss, osteoporosis, and a cluster of dysmetabolic effects that closely mirror the metabolic

syndrome in humans. Understanding how glucocorticoids influence metabolism, and how they synergize with/oppose other regulatory hormones, has become important for minimizing the side effects of chronic glucocorticoid exposure. Glucocorticoids are widely used in Western countries, where ageing- and inflammatory-related conditions are common.

Here, we describe in animal models how glucocorticoid signalling in adipose tissues (white and brown) and in bone contributes to energy homeostasis, nutrient partitioning and insulin sensitivity. Clearly, glucocorticoids have deleterious effects on adipose tissue, especially VAT, that involve insulin resistance and increased hepatic lipid flux. Accumulation of VAT leads to a marked increase in the risk of type 2 diabetes and cardiovascular disease (77, 78). In bone, glucocorticoids may inhibit bone formation, promoting bone loss, via suppression of glucose metabolism. Lastly, recent studies have reported marked effects of sex hormones on the metabolic effects of chronic glucocorticoid exposure, particularly in adipose tissues and the liver. It is possible that glucocorticoid-induced mobilization of energy stores may provide a large source of energy for skeletal muscle activity (and therefore, survival) in males. In the future, elucidating the mechanisms underlying glucocorticoid actions in metabolic tissues will allow us to minimize potential side effects and develop effective new therapeutic agents for metabolic diseases.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

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