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Anna Vali[1,2], Carine Beaupère[1,2], Alya Loubaresse[1,2], Héloïse Dalle[1,2], Bruno Feve[1,2,3], Alexandra Grosfeld[1,2], Marthe Moldes[1,2*]

Affiliations

[1]Sorbonne Université, Inserm, Centre de Recherche Saint-Antoine, CRSA, F-75012 Paris, France

[2]Sorbonne Université, Inserm, Institute of CardioMetabolism and Nutrition, ICAN, F-75013 Paris, France

[3]Sorbonne Université, Inserm, Centre de Recherche Saint-Antoine, CRSA, AP-HP, Hôpital Saint-Antoine, Service Endocrinologie, CRMR PRISIS, 75012 Paris, France

***Corresponding author**: Marthe Moldes, UMR_S938, Inserm, Sorbonne Université, 27 rue Chaligny, 75012 Paris. Tel: +33140011355. E-mail: marthe.moldes@inserm.fr

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Résumé

Les glucocorticoïdes (GC) jouent un rôle majeur dans l'homéostasie métabolique, notamment en régulant l'homéostasie glucido-lipidique et le système immunitaire. Possédant également des propriétés anti-inflammatoires et immunosuppressives, des analogues synthétiques des GC ont été développés et sont largement utilisés pour traiter des états d'inflammation chronique ou encore dans les cas de transplantation d'organes. Les GC font ainsi partie des médicaments les plus prescrits dans le monde. Néanmoins, à fortes doses et à long terme, ils sont à l'origine d'effets secondaires tels qu'un diabète cortico-induit et une lipodystrophie, qui se caractérise par un développement important du tissu adipeux viscéral au détriment des dépôts sous-cutanés.

Plusieurs études ont rapporté des résultats contrastés sur l'invalidation constitutive du récepteur des GC (GR) spécifiquement dans les adipocytes de souris soumises à différents régimes et traitements. Pour pallier les mécanismes compensatoires potentiels lors du développement des tissus adipeux, nous avons généré un modèle murin inductible d'invalidation du GR spécifique de l'adipocyte (AdipoGR-KO) et montré le rôle déterminant du GR adipocytaire dans les altérations métaboliques induites par les GC. Les souris AdipoGR-KO présentent par rapport aux animaux témoins en condition d'hypercorticisme, une amélioration de la tolérance au glucose, de la sensibilité à l'insuline, et du profil lipidique, malgré une expansion massive de l'adiposité. Ce résultat s'explique par une densification de la vascularisation des tissus adipeux, soulignant ainsi le rôle répresseur du GR adipocytaire sur l'expansion saine de ce tissu. Nos travaux ont contribué à démontrer le rôle majeur du GR adipocytaire dans la physiologie et la physiopathologie du tissu adipeux et son impact sur l'homéostasie énergétique.

Abstract

Glucocorticoids (GCs) play an important role in metabolic adaptation, regulating carbohydrate-lipid homeostasis and the immune system. Because they also have anti-inflammatory and immunosuppressive properties, synthetic analogues of GCs have been developed and are widely used in the treatment of chronic inflammatory conditions and in organ transplantation. GCs are among the most commonly prescribed drugs in the world. However, long term and high GCs doses can cause side effects such as GC-induced diabetes and lipodystrophy.

In recent years, a large number of independent studies have reported the effects of constitutive and adipocyte-specific deletion of the GC receptor (GR) in mice under different diets and treatments, resulting in contrasting phenotypes. To avoid potential compensatory mechanisms associated with the constitutive adipocyte GR silencing during adipose tissue development, our team generated an inducible mouse model of GR deletion specifically in the adipocyte (AdipoGR-KO).

Using this mouse model, we were able to demonstrate the critical role of the adipocyte GR in GC-induced metabolic changes. Indeed, under conditions of hypercorticism, AdipoGR-KO mice show an improvement in glucose tolerance and insulin sensitivity, as well as in lipid profile, despite a massive increase in adiposity. This result is explained by a densification of adipose tissue vascularization, highlighting the repressive role of adipocyte GR in the healthy expansion of this tissue.

Our work has largely contributed to the demonstration of the important role of the adipocyte GR in the physiology and pathophysiology of the adipose tissue and its impact on energy homeostasis.

Introduction

Due to their anti-inflammatory and immunomodulatory properties, GCs have been widely developed synthetically and are currently used for the treatment of diseases such as asthma, rheumatoid arthritis, chronic inflammatory digestive diseases or for immunosuppressive purposes in transplanted patients [1]. Today, 0.5-to-1% of the general population uses systemic GCs therapy on a long-term basis (more than 15 mg prednisone per day for more than 60 days) [2]. In Human, prolonged exposure to exogenous or endogenous GCs leads to a Cushing's syndrome, which is associated with a hypercatabolic muscle, bone density loss and skin atrophy, as well as dysregulation of glucose and lipid metabolism [3]. Metabolic events induced by overexposure to GCs action are among the most common and serious adverse effects [2]. These include severe insulin resistance, which can even lead to diabetes as well as dyslipidaemia, hypertension and lipodystrophy [4]. This latter is characterized by an increase in visceral adipose tissue expansion at the expense of subcutaneous adipose tissue [5, 6]. All these complications are associated with an increased risk of cardiovascular events such as myocardial infarction and stroke [2, 7]. It is therefore essential to comprehend and manage GCs side-effects in order to optimize patients' chronic treatment with those molecules [8].

Numerous studies, including ours, identified different molecular players involved in the adverse effects of hypercorticism. This body of literature, which will be discussed herein, aims to pinpoint and counteract signaling pathways misregulated by GCs to improve patients' care.

Glucocorticoid secretion, bioavailabiity and action

Cortisol in Human and corticosterone in rodents are the main natural GCs, derived from cholesterol. The synthesis and release of these hormones are controlled by the hypothalamic-pituitary-adrenal (HPA) axis and follows a circadian rhythm and additionally is triggered by stresses, which can be physical (pain, cold, noise, light changes), metabolic (low blood sugar) or psychological (depression). Release of CRH (corticotrophin-releasing hormone) from the hypothalamic paraventricular nucleus induces transcription of the POMC (proopiomelanocortin) gene, a precursor of ACTH (adrenocorticotrophin hormone). The release of ACTH as a result of post-translational proteolysis of POMC, in the anterior pituitary gland, stimulates steroid hormone production by the adrenal cortex [9]. The balance between GCs stimulation and secretion is maintained by negative feedback control of the corticotropic axis exerted by the binding of GCs to their own receptors in cells of the HPA axis.

GCs are hydrophobic hormones. They enter the cytoplasm by passively crossing the plasma membrane and can bind to two different nuclear receptors, the GC receptor (GR) and the mineralocorticoid receptor (MR), which also binds aldosterone. These two receptors are expressed at different levels in several tissues. In the adipose tissue, although MR is 10 times more affine for GCs than GR, the expression of the *Gr* gene is between 20 and 250 times higher than that of *Mr* in mice and Human, respectively [5, 10]. Upon binding, nuclear receptors undergo conformational changes and translocate to the nucleus, regulating the expression of many genes involved in cellular metabolism, differentiation and inflammation. It is estimated that the GR can transactivate or alternatively transrepress the expression of up to 20% of the genome [5, 9]. In addition, nuclear receptors can exert rapid non-genomic effects in the cytosol, notably by interacting with chaperones or kinases [11].

GCs action are also regulated at the cellular level and upstream of their receptors. This regulation dependents on two microsomal enzymes: 11β-hydroxysteroid dehydrogenase type-1 (11β-HSD-1) and 11β-hydroxysteroid dehydrogenase type-2 (11β-HSD-2) [5]. The 11β-

HSD-1 enzyme is found ubiquitously, but is particularly abundant in liver and adipose tissue. This enzyme with NADP(H)-dependent dehydrogenase activity and reductase activity converts inactive cortisone to active cortisol in Human and 11-deoxycorticosterone to corticosterone in rodents. Conversely, 11β-HSD-2 only has NAD-dependent dehydrogenase activity and catalyzes the conversion of active cortisol to cortisone in Human (and corticosterone to 11-deoxycorticosterone in rodents). The 11β-HSD-2 is mainly located in tissues targeted by aldosterone, such as kidney, colon and salivary glands, where it prevents the action of GCs on the mineralocorticoid receptor. In adipose tissues, 11β-HSD-1 constitutes a local source of cortisol/corticosterone, amplifying the system independently of their circadian plasma variations. Thus, the local concentration of GCs in adipose tissue is 10 to 15 times higher than in the plasma [12].

Glucocorticoid impact on adipose tissue

GCs exert pleiotropic effects on adipose tissue biology. They promote adipogenesis and regulate metabolism of mature adipocytes [13-15]. GCs accelerate adipocyte differentiation by inhibiting preadipocyte proliferation [16] and promoting expression/phosphorylation of early adipogenic transcription factors. This leads to the induction of later adipocyte differentiation factors and potentiates their action [15, 17-20].

Depending on the location of the adipose tissue (deep or superficial), the nutritional and hormonal status, GCs differentially modulate lipogenesis, lipolysis and the secretory capacities of mature adipocytes [5, 21]. While GCs reduce lipogenesis and free fatty acid (FFA) uptake in the basal or fasting state, they promote lipid storage in the fed state by potentiating the effect of insulin on FFA uptake *via* lipoprotein lipase (LPL). GCs act in concert with insulin to increase *de novo* lipogenesis and triglyceride (TG) synthesis by inducing lipogenic enzyme expression [5, 22, 23].

Long term GCs exposure directly affect insulin signaling in the adipocyte by altering insulin receptor substrate-1 and -2 (IRS-1 and -2), leading to a decreased in GLUT4 translocation at the plasma membrane [4, 24]. They stimulate lipolysis through activation of lipase gene expression [22, 25, 26] and through the increase in cAMP level and PKA activity [27, 28]. The activation of the β-adrenergic pathway by GCs leads to an increase in the phosphorylation of lipases and perilipin, thereby promoting lipolysis [28]. These catecholamine-dependent effects are particularly evident in visceral adipose tissue, which is particularly sensitive to lipolytic agents [29]. Furthermore, GCs inhibit the re-esterification of FFA, increasing their release into the bloodstream [30]. Finally, GCs regulate the secretion of several adipokines, such as adiponectin and leptin, which are major regulators of the whole-body insulin sensitivity and insulin secretion [31].

Glucocorticoid action and adipocyte expansion and plasticity

Studies on the 11β-HSD-1 enzyme, which can locally enhance GCs signaling, and on the MR and GR receptors have been the focus of much research in recent years.

A large body of *in vivo* data has confirmed the altered regulation of 11β-HSD-1 in obese adipose tissue and the importance of its role in metabolism. A 2- to 3-fold increase in 11β-HSD-1 activity has been demonstrated in the adipose tissue of Zucker rats [32]. Mice fed with a high fat diet with global 11β-HSD-1 deletion were protected from obesity, dyslipidaemia and glucose intolerance, and had an improved hepatic profile [33]. In addition, these 11β-HSD-1-deficient mice exhibited a healthy expansion of fat depot with enhanced angiogenesis and paradoxically a reduced inflammation of AT [34, 35]. Interestingly, this

model was also resistant to the metabolic side effects of hypercorticism [36-38]. Conversely, overexpression of 11β-HSD-1 specifically in the adipocyte led to increased levels of corticosterone in adipose tissue, visceral obesity, insulin resistance, hypertension and dyslipidaemia [36-38]. Its overexpression in the liver was associated with moderate insulin resistance, hypertension and dyslipidaemia without obesity [39], stressing the detrimental impact of excess GCs particularly in AT.

The relative functional contribution of GR and MR in a given tissue depends on i) their relative abundance, ii) the local concentration of GCs and aldosterone, and iii) the local conversion of active cortisol to cortisone. The expression of the *Nc3c1 (Gr)* and *Nr3c2* (*Mr)* genes is increased in adipose tissues of obese patients and mice, particularly in the visceral adipose tissue [40-43].
Several studies have shown that pharmacological MR blockade has beneficial metabolic effects in ob/ob and db/db genetic models of obesity and in diet-induced obese mice [40, 44-46]. Conditional overexpression of MR in adipocytes and in macrophages resulted in increased body weight, especially fat mass, and the development of insulin resistance and clinical features of metabolic syndrome not only on a high-fat diet [41], but also on a chow diet [47]. However, constitutive or conditional deletion of MR specifically in adipocytes did not protect animals from obesity and glucose dysfunction on a high-fat diet [48, 49], revealing that the beneficial metabolic effects of MR blockade in obese mice was not only due to adipocytes, but also involved other MR-expressing cell types in adipose tissue, such as macrophages. Furthermore, the modest effect of MR on adipose tissue biology in adipocyte-specific MR transgenic models suggest that an alternative molecular player such as GR may be a relevant receptor to target in adipocytes.

The role of the adipocyte GR has been extensively studied in recent years in numerous cellular and mouse models of obesity or GR deficiency. *In vitro*, GR appeared to play a crucial role in the early adipocyte differentiation, whereas *in vivo*, GCs and GR increased and accelerated the development of adipose tissue without being essential [50, 51]. The non-selective GR antagonist Mifepristone (RU486), which blocks GR and the progesterone receptor (PR), prevented obesity and improved glucose tolerance in obese rats [52]. However, constitutive deletion of GR specifically in adipocytes led to divergent phenotypes in terms of weight, adiposity, glucose tolerance or insulin sensitivity when mice were subjected to diet-induced obesity or treatment with corticosterone or the GR agonist, dexamethasone [10, 53-56]. These discrepancies may be due to the experimental methods used as well as to the mouse models of constitutive ablation of the GR, which may lead to an adaptation during the adipose tissue developmental process. In order to overcome potential compensatory mechanisms due to the constitutive deletion of GR in mice, our laboratory has developed an inducible model of adipocyte GR-deficient mice (AdipoGR-KO). When treated with high doses of corticosterone, they exhibited a massive expansion of adiposity, which was paradoxically associated with a protection against glucose intolerance and insulin resistance classically induced by corticosterone [57]. These findings were later corroborated by Hayashi *et al.* on their constitutively-deficient GR model [58]. Lipid storage was greatly increased in the adipose tissue of AdipoGR-KO mice protecting other organs from lipid spillover and improving their plasma lipid profile. Furthermore, the GR-deleted adipose tissue was less inflammatory [57] and showed a large increase in the vascular network associated with a strong induction of VEGFA (vascular endothelial growth factor) expression and of its transcriptional regulator HIF-

1α [59]. Blocking VEGFA action by the fusion protein Aflibercept in combination with the CORT treatment reduced the number of endothelial cells in the adipose tissue of AdipoGR-KO mice and limited the beneficial effects of adipocyte GR deletion by reducing fat mass, insulin sensitivity and allowing GC-induced hepatic steatosis in these mice [59]. Finally, we validated our findings in Human through the use of adipose tissue from patients with Cushing's syndrome (Lipocush cohort) and showed that higher VEGFA expression in the subcutaneous adipose tissue of Cushing's patients was correlated with a better metabolic profile (HOMA-IR and HbA1c). Thus, these results highlight that adipocyte GR is a key player in the metabolic side effects of GCs [59]. It negatively controls adipose tissue expansion and metabolic health by down-regulating the major angiogenic effector VEGFA, inhibiting vascular network development and altering adipocyte adaptation and function.

Conclusion

Our work has been instrumental in demonstrating the important role of the adipocyte GR in the physiology and pathophysiology of adipose tissue and its impact on energy homeostasis. This better understanding of the action of adipocyte GR will therefore help to define future innovative therapeutic strategies to reduce the negative metabolic effects of GCs, such as insulin resistance and hepatic steatosis.

Disclosure of interest

The authors declare that they have no competing interest.

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