Published in final edited form as:

Hypertension. 2015 July ; 66(1): 17–19. doi:10.1161/HYPERTENSIONAHA.115.05148.

What Is the Role of the Adipocyte Mineralocorticoid Receptor in the Metabolic Syndrome?

Celso E. Gomez-Sanchez

Department of Medicine, G.V. (Sonny) Montgomery VA Medical Center and University of Mississippi Medical Center, Jackson

Obesity is an important risk factor for cardiovascular disease, including hypertension, coronary atherosclerosis, congestive heart failure, and stroke, as well as for chronic renal disease.¹ The prevalence of metabolic syndrome in obese patients is high, as they frequently have hypertension, insulin resistance with glucose intolerance or diabetes mellitus, high triglycerides, and low high-density lipoprotein cholesterol that defines the syndrome. The adipocyte has emerged to the forefront of important mediators of the metabolic abnormalities seen in the metabolic syndrome. Many studies have also demonstrated a positive correlation between body mass index and serum aldosterone levels,¹ and aldosterone seems to have an important role in the pathogenesis of the metabolic syndrome by acting through the mineralocorticoid receptor (MR) in several target organs, including adipocytes.^{1,2} Despite these increases in aldosterone, cortisol (human) or corticosterone (rodents) has similar affinity for the MR and is far more abundant, thus may be more important culprits.³ Nonetheless, preclinical studies of antagonism of the MR reverse many features of the metabolic syndrome.²

The roles of the MR and glucocorticoid receptor (GR) in adipocyte differentiation in vivo and in the metabolic syndrome are yet unresolved. The article by Urbanet et al⁴ in this issue aims to clarify the role of the MR in adipocyte differentiation, obesity, and the mechanisms by which the MR activation leads to adipocyte differentiation using an adipose-specific inducible transgenic model of MR overexpression. Historically, the MR was initially thought to be expressed exclusively in ion and water transport epithelia of the renal tubules, colon, salivary glands, and sweat glands. However, shortly after its cloning, it was confirmed that the MR was also expressed in nonepithelial tissues, including the heart, vessels, and brain (where it was called the type I corticosteroid receptor). Two MR mRNA isoforms arising from alternative promoter utilization have been identified. Transgenic mice with the P1 MR promoter driving the SV40 large T antigen develop malignant liposarcomas originating from brown adipose tissue. Cell lines derived from these tumors express the MR and can be differentiated into brown adipocytes.² This was one of the first demonstrations that the MR had a role in adipose tissue. Further studies confirmed the role of MR in white adipocytes.² Glucocorticoid excess in Cushing syndrome is associated with centripetal obesity

Correspondence to Celso E. Gomez-Sanchez, G.V. (Sonny) Montgomery VA Medical Center, 1500 E. Woodrow Wilson Dr, Jackson, MS 39216. Cgomez-sanchez@umc.edu.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Disclosures: None.

demonstrating the role of glucocorticoid excess in the growth and differentiation of adipocytes. The similar distribution of adipose tissue suggested that glucocorticoids also had a role in the metabolic syndrome. The receptors involved in these actions were initially believed to be GR. Although both MR and GR are expressed in adipose tissue, expression of GR is several 100-fold higher than the MR. However, using an in vitro system to study the differentiation of the mouse preadipocyte cell lines 3T3-L1 or 3T3-F442A, aldosterone, was found to promote the time, dose, and MR-dependent acquisition of the adipocyte phenotype with the induction of the relevant transcription factors and adipose genes (Figure). These events were inhibited by the concurrent incubation with the MR antagonist spironolactone.⁵ In human preadipocytes, knockdown of the GR, but not the MR, blocked the proadipogenic actions of cortisol.⁶ Both GR and MR had roles in regulating leptin expression in these cells, but the GR had a more important role in mediating the actions of cortisol in adipogenesis and adipokine production.⁶ However, other studies have shown different results.^{5,7} Dexamethasone was found to inhibit, whereas aldosterone stimulated, the expression of interleukin 6, monocyte chemoattractant protein-1, tumor necrosis factor- α , chemerin, and leptin in mouse white adipocytes.⁷ Adipocytes in which the MR is deleted fail to accumulate lipids, whereas those with the GR deleted exhibit mildly impaired adipogenesis.⁷ Extensive data support the role of the MR in adipogenesis,² notwithstanding data to the contrary suggesting a primary role of the GR reviewed above,⁶ including the paradoxical resistance to high-fat diet-induced obesity in transgenic mice overexpressing the MR driven by its proximal promoter, P1.⁸

Mature adipocytes in both the human and mouse obese animals are increased in comparison with lean controls. The work by Urbanet et al⁴ demonstrated that MR expression is increased in adipose tissues of obese compared with lean humans and that the increase is greater in visceral compared with subcutaneous adipose tissue. Similarly, expression of both subcutaneous and visceral adipose tissue is increased in obese db/db compared with lean db/+ control mice.⁴ To further clarify the role of increased MR expression in adipocytes, they created a transgenic mouse with conditional and tetracycline-inducible model of overexpression of the MR in adipocytes. The Adipo-MROE mouse progressively gains body weight and visceral fat compared with control-MR mice and displays features of the metabolic syndrome, including insulin resistance, hypertriglyceridemia, hypercholesterolemia, but no change in blood pressure. High-fat diet exacerbated the impairment of insulin response. Aldosterone levels in the Adipo-MROE mice were not different with the controls. Transcriptional analysis revealed 101 upregulated genes and 246 downregulated genes. The gene for prostaglandin D2 synthase (*PTGDS*), an enzyme involved in adipose tissue pathophysiology, was among those upregulated. *PTGDS* is expressed in other tissues as well as in adipose tissue. Urbanet et al demonstrated that *PTGDS* is a key factor of aldosterone action on adipocytes, as specific inhibition of *PTGDS* blunted the adipogenic effect of aldosterone. However, the involvement of the MR-responsive *PTGDS* transcript fails to explain the discrepant finding that the *PTGDS* knockout mouse is a model of accelerated insulin resistance, glucose intolerance, and obesity (Figure).⁹ Although this candidate gene approach of concentrating on a single upregulated gene seems to have led to an important discovery, there are many other

transcripts, some coding for yet unidentified entities that may also be important and should be studied.

Although most evidence, including the article by Urbanet et al,⁴ supports the role of the MR in adipogenesis, the nature of the ligand is less certain. Cortisol and corticosterone have greater affinity for the MR than for the GR and circulate in 100 (as free steroid) to a 1000 (total steroid) times the concentration of aldosterone, thus are the preferred ligands for the MR. In transporting epithelia of the kidney, colon, and others, selectivity for aldosterone is accomplished by the coexpression of the 11 β -hydroxysteroid dehydrogenase 2 (11 β -HSD2) which converts the active glucocorticoids cortisol or corticosterone into the inactive steroids cortisone or 11-dehydrocorticosterone. Adipose tissue express low levels of 11 β -HSD2 and high levels of the 11 β -HSD1, which functions primarily as an oxido reductase converting the inactive cortisone or 11-dehydrocorticosterone into the active cortisol or corticosterone, thus amplifying the activity of these steroids by recycling them from the circulation (Figure).³ Specific 11 β -HSD1 inhibitors suppressed adipocyte differentiation induced by cortisone and in vivo suppressed the 11 β -HSD1 activity in liver and fat and improved insulin sensitivity.³ Cortisone circulates at $\approx 1/10$ the concentration of cortisol, but the affinity for CBG is also $\approx 1/10$ that of cortisol, thus free concentrations of cortisone in tissue should be approximately the same, resulting in a significant augmentation in the concentration in cells expressing 11 β -HSD1. This is likely the reason for the effectiveness of in vivo antiadipogenic effects of 11 β -HSD1 inhibitors.³

Plasma aldosterone levels in obesity increase and correlate with body mass index and blood pressure, but are still within the normal range.¹ Most in vitro studies of the effect of aldosterone on preadipocyte differentiation to adipocyte have used supraphysiological concentrations of aldosterone (10 nmol/L) compared with aldosterone concentrations in normal or obese individuals (0.1–0.4 nmol/L) or even those in patients with primary aldosteronism (0.3–1 nmol/L). The in vivo tissue concentrations of free cortisol (plus the contribution of recycled cortisone) are closer to those used in many of the adipocyte differentiation studies.^{6,7} Briones et al¹⁰ have recently demonstrated that the 3T3-L1 adipocyte cell line and mature adipocytes isolated from human and mouse adipose tissue express the last enzyme in the biosynthesis of aldosterone (CYP11B2) and the cells secrete aldosterone in response to angiotensin II (Figure). The angiotensin II effects were blunted by coincubation with a angiotensin receptor antagonist (candesartan) and inhibitors of calcineurin. The CYP11B2 enzyme inhibitor FAD286 also blunted adipocyte differentiation. Candesartan treatment in db/db mice reduced plasma aldosterone and CYP11B2 expression.¹⁰ These studies suggest that aldosterone production by the adipocyte regulates adipocyte differentiation through an autocrine or paracrine effect. Adipose tissue also secretes an unidentified factor that stimulates adrenal aldosterone production.¹⁰ Adipocyte thus seems to enhance further differentiation of new adipocytes by increasing aldosterone by 2 different mechanisms, stimulation of adrenal production by an adipocyte-derived substance and by the extra-adrenal synthesis of aldosterone by adipocytes acting in an autocrine–paracrine manner and provide a link between aldosterone-obesity and diabetes mellitus.

Acknowledgments

Sources of Funding: Dr Gomez-Sanchez is supported by National Heart, Lung, and Blood Institute grant RO1HL27255.

References

1. Calhoun DA, Sharma K. The role of aldosteronism in causing obesity-related cardiovascular risk. *Cardiol Clin.* 2010; 28:517–527. DOI: 10.1016/j.ccl.2010.04.001 [PubMed: 20621254]
2. Marzolla V, Armani A, Feraco A, De Martino MU, Fabbri A, Rosano G, Caprio M. Mineralocorticoid receptor in adipocytes and macrophages: a promising target to fight metabolic syndrome. *Steroids.* 2014; 91:46–53. DOI: 10.1016/j.steroids.2014.05.001 [PubMed: 24819992]
3. Morton NM. Obesity and corticosteroids: 11beta-hydroxysteroid type 1 as a cause and therapeutic target in metabolic disease. *Mol Cell Endocrinol.* 2010; 316:154–164. DOI: 10.1016/j.mce.2009.09.024 [PubMed: 19804814]
4. Urbanet R, Nguyen Dinh Cat A, Feraco A, Venteclef N, El Moghrabi S, Sierra-Ramos C, Alvarez de la Rosa D, Adler GK, Quilliot D, Rossignol P, Fallo F, Touyz RM, Jaisser F. Adipocyte mineralocorticoid receptor activation leads to metabolic syndrome and induction of prostaglandin D2 synthase. *Hypertension.* 2015; 66:149–157. DOI: 10.1161/HYPERTENSIONAHA.114.04981 [PubMed: 25966493]
5. Caprio M, Fève B, Claës A, Viengchareun S, Lombès M, Zennaro MC. Pivotal role of the mineralocorticoid receptor in corticosteroid-induced adipogenesis. *FASEB J.* 2007; 21:2185–2194. DOI: 10.1096/fj.06-7970com [PubMed: 17384139]
6. Lee MJ, Fried SK. The glucocorticoid receptor, not the mineralocorticoid receptor, plays the dominant role in adipogenesis and adipokine production in human adipocytes. *Int J Obes (Lond).* 2014; 38:1228–1233. DOI: 10.1038/ijo.2014.6 [PubMed: 24430397]
7. Hoppmann J, Perwitz N, Meier B, Fasshauer M, Hadaschik D, Lehnert H, Klein J. The balance between gluco- and mineralo-corticoid action critically determines inflammatory adipocyte responses. *J Endocrinol.* 2010; 204:153–164. DOI: 10.1677/JOE-09-0292 [PubMed: 19939912]
8. Kuhn E, Bourgeois C, Keo V, Viengchareun S, Muscat A, Meduri G, Le Menuet D, Fève B, Lombès M. Paradoxical resistance to high-fat diet-induced obesity and altered macrophage polarization in mineralocorticoid receptor-overexpressing mice. *Am J Physiol Endocrinol Metab.* 2014; 306:E75–E90. DOI: 10.1152/ajpendo.00323.2013 [PubMed: 24222670]
9. Evans JF, Islam S, Urade Y, Eguchi N, Ragolia L. The lipocalin-type prostaglandin D2 synthase knockout mouse model of insulin resistance and obesity demonstrates early hypothalamic-pituitary-adrenal axis hyperactivity. *J Endocrinol.* 2013; 216:169–180. DOI: 10.1530/JOE-12-0275 [PubMed: 23151358]
10. Briones AM, Nguyen Dinh Cat A, Callera GE, Yogi A, Burger D, He Y, Corrêa JW, Gagnon AM, Gomez-Sanchez CE, Gomez-Sanchez EP, Sorisky A, Ooi TC, Ruzicka M, Burns KD, Touyz RM. Adipocytes produce aldosterone through calcineurin-dependent signaling pathways: implications in diabetes mellitus-associated obesity and vascular dysfunction. *Hypertension.* 2012; 59:1069–1078. DOI: 10.1161/HYPERTENSIONAHA.111.190223 [PubMed: 22493070]

Figure.

The mineralocorticoid receptor (MR) action in preadipocytes and adipocytes. Cytosolic MR is activated by both aldosterone and cortisol. The source of aldosterone is both from the circulation and synthesis in the adipocyte by the stimulation of aldosterone synthase (CYP11B2) by angiotensin II (Ang II). Most circulating cortisol (F) is bound to corticosteroid-binding protein (CBG); $\approx 10\%$ is free to diffuse into the adipocyte. Cortisone (E) circulates at $\approx 10\%$ that of F, but is less tightly bound to CBG and also diffuses into the adipocyte where it is reduced by 11β -hydroxysteroid dehydrogenase I (11HSD1) to F, increasing the intracellular concentration of F which binds the MR. Ligand-bound MR are translocated to the nucleus where they stimulate gene transcription, including the prostaglandin D2 synthase (*PTGDS*) gene and others responsible for preadipocyte differentiation into the adipocyte and accumulation of lipid droplets. The role of the glucocorticoid receptor is less certain.