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

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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. 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, 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. 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. Nonetheless, preclinical studies of antagonism of the MR reverse many features of the metabolic syndrome.

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 al 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. 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. Glucocorticoid excess in Cushings syndrome is associated with centripetal obesity 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. In human preadipocytes, knockdown of the GR, but not the MR, blocked the proadipogenic actions of cortisol. 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. However, other studies have shown different results. Dexamethasone was found to inhibit, whereas aldosterone stimulated, the expression of interleukin 6, monocyte chemottractant protein-1, tumor necrosis factor-α, chemerin, and leptin in mouse white adipocytes. Adipocytes in which the MR is deleted fail to accumulate lipids, whereas those with the GR deleted exhibit mildly impaired adipogenesis. Extensive data support the role of the MR in adipogenesis, notwithstanding data to the contrary suggesting a primary role of the GR reviewed above, including the paradoxical resistance to high-fat diet–induced obesity in transgenic mice overexpressing the MR driven by its proximal promoter, P1.

Mature adipocytes in both the human and mouse obese animals are increased in comparison with lean controls. The work by Urbanet et al 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. 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 inhi-
bition of PTGDS blunted the adipogenic effect of aldosterone.
However, the involvement of the MR-responsive PTGDS tran-
script fails to explain the discrepant finding that the PTGDS
knockout mouse is a model of accelerated insulin resistance,
glucose intolerance, and obesity (Figure). Although this can-
didate 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 enti-
ties that may also be important and should be studied.

Although most evidence, including the article by Urbanet
et al, 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 concentra-
tion of aldosterone, thus are the preferred ligands for the MR.
In transporting epithelia of the kidney, colon, and others, selec-
tivity for aldosterone is accomplished by the coexpression of
the 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) which
converts the active glucocorticoids cortisol or corticosterone
into the inactive steroids cortisone or 11-dehydrocorticoste-
one. Adipose tissue express low levels of 11β-HSD2 and high
levels of the 11β-HSD1, which functions primarily as an oxido
reductase converting the inactive cortisone or 11-dehydrocorti-
costerone into the active cortisol or corticosterone, thus
amplifying the activity of these steroids by recycling them
from the circulation (Figure). Specific 11β-HSD1 inhibitors
suppressed adipocyte differentiation induced by cortisone and
in vivo suppressed the 11β-HSD1 activity in liver and fat and
improved insulin sensitivity. Cortisone circulates at ≈1/10 the
concentration of cortisol, but the affinity for CBG is also ≈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 the cells expressing 11β-
HSD1. This is likely the reason for the effectiveness of in vivo
antiadipogenic effects of 11β-HSD1 inhibitors.

Plasma aldosterone levels in obesity increase and corre-
late with body mass index and blood pressure, but are still
within the normal range. 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 con-
tribution of recycled cortisone) are closer to those used in
many of the adipocyte differentiation studies. Briones et al
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 blunt by coinubcation 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. These studies
suggest that aldosterone production by the adipocyte regulates
differentiation through an autocrine or paracrine effect. Adipose
tissue also secretes an unidentified factor that stimulates
adrenal aldosterone production. 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.

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);
≈10% is free to diffuse into the adipocyte. Cortisone (E) circulates at ≈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
translocates 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.
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None.

References


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