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Review

The role of the mineralocorticoid receptor in adipocyte biology and fat metabolism

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ABSTRACT

Aldosterone controls blood pressure by binding to the mineralocorticoid receptor (MR), a ligand-activated transcription factor which regulates critical genes controlling salt and water homeostasis in the kidney. In recent years, inappropriate MR activation has been shown to trigger deleterious responses in various tissues, including vessels, heart and brain, hence promoting vascular inflammation, cardiovascular remodeling, endothelial dysfunction, and oxidative stress. Moreover, epidemiological studies have shown a clear association between aldosterone levels and the incidence of metabolic syndrome. In particular, recent work has revealed functional MRs in adipose tissue, where they mediate the effects of aldosterone and glucocorticoids, displaying important and specific functions involving adipose differentiation, expansion and proinflammatory capacity. This recent evidence finally moved MR out of the shadow of the glucocorticoid receptor (GR), which had previously been considered the only player mediating corticosteroid action in adipose tissue. This has opened a new era of research focusing on the complexity and selectivity of MR function in adipocyte biology.

The aim of this review is to summarize the latest concepts on the role of MR in white and brown adipocytes, and to discuss the potential benefits of tissue-selective MR blockade in the treatment of obesity and metabolic syndrome.

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1. Introduction

The wider distribution of the mineralocorticoid receptor (MR) was identified from the studies in the early 1970s when type 1 and type 2 corticosteroid receptors were revealed in a range of tissues. MR expression was considered to be restricted to polarized tight epithelia, where it mediates aldosterone-dependent transepithelial sodium transport (Marver et al., 1974). Classical epithelial

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tissues, including distal convoluted tubules and cortical collecting ducts (Krozowski et al., 1989; Lombes et al., 1990), distal colon of rat (Pressley and Funder, 1975), salivary (Funder et al., 1972) and sweat glands (Kenouch et al., 1994), were found to express MR transcripts and protein. MR expression has been more recently shown in different target epithelia such as airway epithelia of the lung (Krozowski and Funder, 1981), eyes (Mirshahi et al., 1997; Zhao et al., 2010), and skin (Kenouch et al., 1994; Sainte-Marie et al., 2007; Mitts et al., 2010).

MR possesses a similar affinity for aldosterone and the physiological glucocorticoids (cortisol and corticosterone); in particular, its affinity for cortisol (in human) and corticosterone (in rodents) is >10-fold higher than that of the GR itself (Arriza et al., 1987). Since glucocorticoids circulate at 100- to 1000-fold higher concentrations than those of aldosterone (0.1–1 nM), aldosterone selectivity for the MR in epithelial tissue requires the intracellular enzymatic action of 11β-hydroxysteroid dehydrogenase type 2 (11HSD2), which transforms glucocorticoids into inactive metabolites (cortisone, 11-dehydrocorticosterone) that have weak or no affinity for the MR (Edwards et al., 1988; Funder et al., 1988). Besides 11HSD2, which provides the most potent MR-protective system in epithelial tissues, other mechanisms protecting MR activation by glucocorticoids may occur in non-epithelial tissues. First, levels of bioactive cortisol reaching the mineralocorticoid target cells are in part reduced by their binding to plasma albumin and to corticosteroid binding globulin: for this reason only 10% of cortisol is free in the plasma, whereas aldosterone circulates mainly in a free form. Furthermore, increasing evidence supports the hypothesis that a change in the redox state of the cell can increase MR signaling mediated by glucocorticoids (Nagase et al., 2007; Wang et al., 2008; Young, 2008). Therefore, cellular context appears to determine MR specificity and activity.

A new exciting area of MR biology has begun following the identification of MR in "non-epithelial" target tissues, where expression of 11HSD2 is virtually absent or extremely low (Funder, 2005), and glucocorticoids represent its major ligands. MR protein has been detected in the hippocampus and in the hypothalamus (Moguilewsky and Raynaud, 1980; Han et al., 2005), as well as in cardiomyocytes and large vessels (Lombes et al., 1992). In addition, expression of MR has been shown in macrophages/monocytes (Armanini et al., 1985), where it plays an important role in mediating tissue remodeling and vascular responses induced by chronic mineralocorticoid/salt treatment (Rickard et al., 2009). Interestingly, selectively deletion of MR from macrophages protects mice from the development of cardiac fibrosis and hypertension.

Finally, several studies have implicated MR signaling in adipocyte biology (Urbanet et al., 2010; Caprio et al., 2007, 2011; Rondinone et al., 1993). Importantly, given the lack of significant 11HSD2 expression and activity in the adipocyte, physiological glucocorticoids, which circulate at 100- to 1000-fold higher concentrations than those of aldosterone, very likely represent the main endogenous ligand of the MR.

This review will focus on the major roles and potential implications of MR signaling in the biology of adipose tissue differentiation and metabolism, its pro-inflammatory capacity, and cross talk with the adrenal gland.

2. MR signaling in adipose differentiation: white and brown adipocytes

Adipose tissue is now regarded as a distinct organ, characterized by a marked cellular heterogeneity, that comprises adipocytes, preadipocytes, fibroblasts, endothelial cells, immune cells and multipotent stem cells. In addition to mature adipocyte, fat tissue is composed of small blood vessels, nerve tissue, fibroblasts and preadipocytes in various stages of development (Bjorntorp and Sjostrom, 1979; Armani et al., 2010). Preadipocytes have the ability to proliferate and differentiate into mature adipocytes, conferring upon adipose tissue a constant functional plasticity, which determines its ability to expand in several physiological and pathological conditions (Sethi and Vidal-Puig, 2007). Adipose tissue is represented by subcutaneous and visceral depots. Subcutaneous adipose tissue (SCAT) is in continuity with the dermal adipose tissue and it is not restricted to a fixed area but appears as a continuous layer under the skin. Visceral adipose tissue (VAT) is located mainly around the internal organs, within the abdominal cavity and the thorax.

In mammals, two distinct types of fat have been described, white adipose tissue (WAT) and brown adipose tissue (BAT). This latter tissue was considered to be essentially nonexistent and without physiologic relevance in adults for many years. Today the scientific community pays much more attention to BAT given the demonstration that BAT is present in substantial amounts in adult humans and metabolically active (Marken Lichtenbelt et al., 2009; Virtanen et al., 2009; Cypess et al., 2009; Saito et al., 2009; Zingaretti et al., 2009). Brown and white adipocytes represent two completely different cell phenotypes and are found to coexist in the context of the adipose organ. Their relative amount depends upon several factors, such as age, gender, environmental temperature, nutritional status and anatomical localization (Cinti, 2009b; Frontini and Cinti, 2010). WAT secretes a number of hormones involved in pleiotropic functions, such as feeding behavior, glucose and lipid metabolism, inflammation and coagulation. Its main function is to safely store and release triglycerides (Ahima and Flier, 2000). On the other hand, BAT has evolved to safely dissipate energy in the form of heat, hence it is involved in thermoregulation in rodents (Nicholls and Locke, 1984) and humans (Champigny and Ricquier, 1996).

The first evidence describing an important role of MR in BAT was demonstrated by Zennaro et al. (1998). The authors developed transgenic mouse models expressing the SV40 large T antigen (TAg) under the control of each of the two promoters of the human MR gene (P1 or P2), and showed that the human MR P1 promoter was transcriptionally active in brown adipocytes, given that the animals developed malignant hybernoma (brown fat tumor). The T37i cell line was then derived from the hibernoma of these transgenic mice. Interestingly, T37i cells are suitable for the study of brown adipose differentiation *in vitro*, since they have a fibroblast-like appearance under basal conditions, and display striking morphological changes following treatment with insulin and triiodothyronine, two known positive regulators of adipogenesis. Importantly, aldosterone treatment induced a significant increase in triglyceride accumulation, along with increased expression of adipogenic genes such as lipoprotein lipase (LPL), peroxisome proliferator-activated receptor (PPARγ) and adipocyte-specific fatty acid binding protein (aP2) (Zennaro et al., 1998; Penfornis et al., 2000). These results demonstrate a major involvement of MR in promoting brown adipose differentiation. Importantly, later studies using these cells showed that aldosterone inhibited expression and function of uncoupling protein-1 (UCP-1), a mitochondrial protein that plays a critical role in the regulation of thermogenesis and energy expenditure, thus promoting the adipose differentiation process, and preventing the metabolic switch toward heat production through inhibition of the expression of UCPs (Viengchareun et al., 2001). Similar data were obtained using immortalized brown adipocytes (Kraus et al., 2005). Interestingly, MR signaling in BAT appears to act as a pivotal signal favoring lipid storage at the expense of heat production, hence promoting in brown adipocytes a specific function of white adipocytes (Fig. 1).

These observations have shifted the attention of researchers to the potential role of MR in white adipose cells, where MR gene expression is known to be induced during adipose conversion (Fu

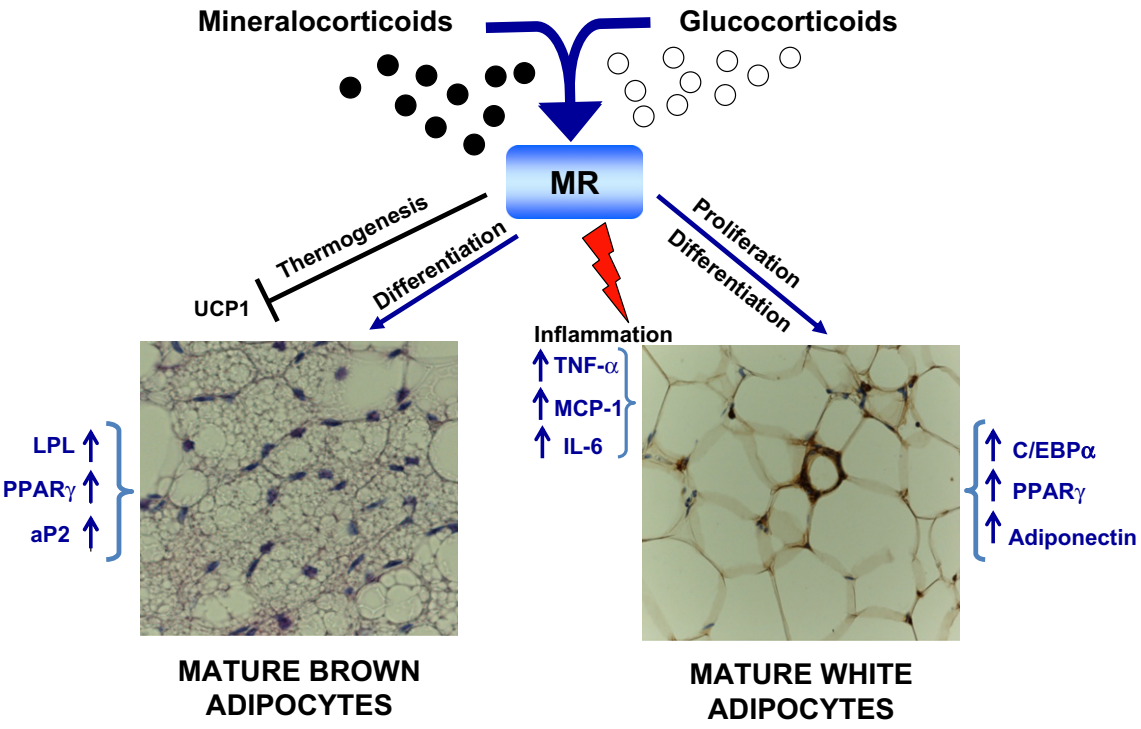

Fig. 1. Important role of MR activation in white and brown fat cell differentiation and function. In brown preadipocytes, MR activation increases expression of adipogenic genes such as LPL, PPARγ and aP2, inducing the accumulation of intracytoplasmic lipid droplets and promoting cell differentiation. Importantly, aldosterone inhibits expression and function of uncoupling protein-1 (UCP-1), thus promoting the adipose differentiation process, and prevents thermogenesis. In white preadipocyte, MR activation induces cell proliferation and subsequently triggers the adipogenic transcriptional machinery, up-regulating C/EBPα and PPARγ gene expression, with subsequent increase in intracellular triglyceride accumulation and adipokines expression. Moreover, MR activation induces the expression of pro-inflammatory genes such as TNF-α, IL-6 and MCP-1, favoring macrophage infiltration and providing the environmental conditions for inflammation.

et al., 2005). While pioneering studies suggested that aldosterone is able to promote adipogenesis (Hauner et al., 1989; Rondinone et al., 1993), more recent studies demostrated a critical role for the MR in 3T3-L1 adipose differentiation induced both by mineralocorticoids and glucocorticoids (Caprio et al., 2007, 2011). In fact, chronic exposure to aldosterone in 3T3-L1 and 3T3-F442A cells induced remarkable changes in morphological, biochemical and molecular markers of adipose differentiation, specifically through activation of the MR. However, due to very low 11HSD2 expression in the adipocyte, and considering the overwhelming prevalence of circulating glucocorticoids in the plasma, the role of aldosterone *in vivo* as a pro-adipogenic factor is unlikely to be physiologically relevant. On the other hand, given the prevalent occupancy of adipose tissue MR by glucocorticoids *in vivo*, the MR could play a major role in mediating glucocorticoid-induced adipose differentiation. Consistent with this hypothesis, transient knock-down of MR can significantly inhibit dexamethasone-induced 3T3-L1 adipose conversion, whereas GR down-regulation does not, indicating that MR is the principal contributor to corticosteroid-induced adipogenesis (Caprio et al., 2007). That the MR may be acting as a glucocorticoid receptor in adipose tissue is of relevance to several pathophysiological settings. For example, adipose tissue-specific amplification of cortisol production in transgenic mice, via overexpression of the enzyme 11HSD1, which reactivates glucocorticoids from inactive 11-keto forms, results in the typical phenotype of full metabolic syndrome, including central obesity, glucose intolerance, insulin resistance-diabetes and hypertension (Masuzaki et al., 2001). In contrast, glucocorticoid inactivation (11HSD1 knock-out mice or 11HSD2 overexpressing animals) is associated with resistance to metabolic dysfunction and diet-induced obesity (Kershaw et al., 2005). In the view of these results, it is tempting to speculate that excessive activation of the adipocyte MR by glucocorticoids may play a role in adipocyte dysfunction, in addition to the GR. Adipose tissue-specific inactivation of MR and/or GR should help to decipher the respective roles of these two nuclear receptors in the development and function of subcutaneous and visceral fat.

We have also recently confirmed that pharmacological blockade of the MR inhibits critical pathways controlling adipose differentiation in 3T3-L1 cells, via inhibition of clonal expansion, a phase of active DNA synthesis following cell confluence, and by interfering with the transcriptional control of adipose conversion through inhibition of PPARγ expression (Caprio et al., 2011). Importantly, we showed that MR antagonism is able to block adipocyte differentiation *ex vivo* also in human primary preadipocytes from different fat depots, giving the MR a clearly relevant role in the pathophysiology of adipose dysfunction in humans.

It is now well documented that, in particular situations, mature white adipocytes (characterized by a single lipid droplet that accounts for about 90% of their cell volume) can transdifferentiate into brown adipocytes, containing several small lipid droplets, through the acquisition of specific intermediate phenotypes (paucilocular adipocytes) (Barbatelli et al., 2010). Importantly, acquisition of brown adipocyte phenotype is associated to resistance to obesity and to inflammation. Differentiation of brown to white adipocytes, in contrast, reduces the critical cell size required for triggering cell death due to fragility of the membrane, which in turn promotes inflammation and insulin resistance (Cinti, 2009a). The role of MR activation in these processes is still unclear and relatively unexplored (Fig. 1).

3. MR activation contributes to adipose tissue inflammation

Inflammation of adipose tissue is considered a hallmark of obesity, given the reciprocal correlation between adipose expansion

and macrophage recruitment (Xu et al., 2003; Murano et al., 2008). Adipose tissue can be considered a "bona fide" endocrine organ, in that it is able to secrete several hormones involved in the regulation of metabolic functions. Among these, adipokines, together with free fatty acids, contribute to the development of an inflammatory state that is believed to underlie the insulin-resistance of obesity (Wellen and Hotamisligil, 2005). The main pathogenic factor in the metabolic syndrome is the central obesity that it is characterized by the accumulation of both SCAT and VAT. However, the excess deposition of VAT appears to play a more significant pathogenic role (Bjorntorp, 1991; Despres and Lemieux, 2006). VAT expansion drives adipose tissue dysfunction through the release of proinflammatory adipokines that, via their direct access to the liver via portal vein, can have a major effect on inflammatory processes (Wajchenberg, 2000). On the other hand, SCAT produces higher levels of protective substances, such as leptin and adiponectin, and is less sensitive to glucocorticoids, which is in part due to the lower expression of GR (Rebuffe-Scrive et al., 1985). Hence SCAT could play a protective role in the metabolic syndrome.

Changes in adipose mass associated with obesity have been linked with *a chronic low-grade* inflammation, characterized by altered production of adiponectin and PPARγ (Berg and Scherer, 2005; Wellen and Hotamisligil, 2005), with a concomitant increase in biological markers of inflammation such as tumor necrosis factor-α (TNF-α), monocyte chemoattractant-1 (MCP-1), and plasminogen activator inhibitor type 1 (PAI-1) (Neels and Olefsky, 2006). In genetically obese *db/db* mice, Guo et al. (2008) observed an increased adipose tissue expression of PAI-1, CD-68, leptin and pro-inflammatory cytokines TNF-α and MCP-1 with a concomitant reduction of PPARγ and adiponectin, compared to lean control mice. Importantly, pharmacological treatment with the selective MR antagonist eplerenone for 16 weeks reversed all obesity-related changes in adipose tissue gene expression.

Similarly, acute effects (3 weeks) of eplerenone administration in *db/db* and *ob/ob* mice also showed improved insulin sensitivity through the reduction of ROS and the suppression of infiltration of adipose tissue macrophages. Again, MR antagonism restored the dysregulation in adipose gene expression in both models (Hirata et al., 2009). These works confirm that genetic obesity in mice promotes dysregulation of adipose tissue endocrine function, and that MR activation is directly implicated in these events.

The enzyme 11HSD1 plays a crucial role in determining intracellular glucocorticoid levels by regenerating active glucocorticoid from inactive metabolites, and works as a tissue-specific amplifier of glucocorticoid action (Walker and Andrew, 2006). Importantly, increased levels of 11HSD1 transcripts in adipose tissue of genetically obese mice were also observed, and MR antagonism was able to restore them to normal levels, with a subsequent reduction in availability of active glucocorticoids as MR ligands (Hirata et al., 2009). This represents a supplementary mechanism, which may contribute to the remarkable improvement in adipose tissue inflammation following treatment with MR antagonists.

Adipocyte size represents another significant morphological parameter that can directly influence the pattern of adipokine secretion. In particular, secretion of pro-inflammatory adipokines is significantly higher in large adipocytes compared with small or medium-sized adipocytes (Skurk et al., 2007). Interestingly, Hirata et al. (2009) showed that MR antagonism can reduce the total number of hypertrophic adipocytes, with a concomitant increase in small adipocytes, without any net effect on the WAT weight. These data suggest that MR signaling directly controls the degree of adipocyte hypertrophy, which in turn has direct effects on its secretory capacity. Such an important observation may explain the overall improvement in function of adipose tissue observed after MR antagonism.

Recent data have also shown that aldosterone is able to inhibit insulin-induced glucose uptake via degradation of insulin receptor substrate (IRS) proteins in 3T3-L1 cells. The authors suggested that induction of ROS by aldosterone triggers the activation of TORC1 (target of rapamycin complex 1) and IKKβ (IκB kinase β) pathways, which are known to promote the degradation of IRS proteins and thereby inhibit insulin action (Wada et al., 2009). This study suggests that inhibition of insulin signaling is mainly mediated by GR, given that GR antagonism, but not MR antagonism, restored insulin signaling. In fact, it should also be noted that the very high doses of aldosterone (1–10 μM) used in these experiments are sufficient for GR activation.

Finally, it has been observed that selective MR stimulation of mature white adipocytes with low doses of aldosterone (in the physiologic range) induced gene expression of pro-inflammatory adipokines interleukin-6 (IL-6) and PAI-1; in contrast, selective GR stimulation significantly suppressed gene expression of MCP-1 and TNF-α (Hoppmann et al., 2010). These results confirm previous reports showing that aldosterone treatment increased the mRNA levels of IL-6, TNF-α and MCP-1 in undifferentiated 3T3-L1 pre-adipocytes (Guo et al., 2008).

It is thus evident that MR activation in adipose tissue plays a causal role in promoting an inflammatory state (Fig. 1). On the other hand GR activation has marked anti-inflammatory effects in addition to a well documented pathophysiological role in insulin resistance, by facilitating the degradation of IRS proteins and through the alteration of physiological adipokine secretion (Wada et al., 2009; Hoppmann et al., 2010).

4. Cross-talk between adipose tissue and the adrenal gland

Obesity, and in particular accumulation of central fat, appears to play a key role in the pathophysiology of metabolic disorders and is strongly associated with hyperactivity of the hypothalamic-pituitary-adrenal axis (Weaver et al., 1993; Bjorntorp, 1997; Duclos et al., 2001). Importantly, hypertension and obesity are frequently associated with 65-78% of hypertension attributed to obesity in the Framingham study (Garrison et al., 1987), and elevated serum aldosterone levels have been reported in obese patients with associated hypertension (Licata et al., 1994; Thakur et al., 2001). Furthermore, two cross-sectional studies have demonstrated that higher aldosterone concentrations are also associated with a greater prevalence of the metabolic syndrome (Kidambi et al., 2007; Ingelsson et al., 2007). Several mechanisms have been proposed to explain this association, which may depend upon activation of the systemic renin–angiotensin–aldosterone system (RAAS) and oxidative stress (Funder, 2007). In fact, increased reactive oxygen species generation and enhanced MR signaling have been shown to accelerate diastolic dysfunction and renal damage in spontaneously hypertensive rats, a valuable model of metabolic syndrome (Nagase et al., 2007; Matsui et al., 2008).

Activation of the RAAS is one of the key mechanisms involved in obesity-associated hypertension. In fact, all components of the system are increased in obese versus lean individuals (Engeli et al., 2005). In transgenic mice overexpressing angiotensinogen, increased circulating levels of angiotensin II and aldosterone were observed, both of which are involved in the development of hypertension (Yang et al., 1994). An increasing number of studies also support the presence of a functional renin–angiotensin-system (RAS) in adipose tissue, which may play a crucial paracrine role in the function of adipocyte development and metabolism (Engeli et al., 2003). Adipose RAS may have a direct causal role in the development of arterial hypertension in obese patients; however this hypothesis is still under debate since it has been observed that

angiotensinogen secretion by adipose tissue is not associated with body fat mass, blood pressure, or fat cell size in cultured adipocytes from obese subjects (Prat-Larquemin et al., 2004). Conversely, it has been reported that weight loss is accompanied by a down-regulation of all components of the adipose RAS, with a subsequent reduction of plasma angiotensinogen levels, and a decrease in systolic blood pressure in obese postmenopausal women (Engeli et al., 2005). Another report showed increased plasma levels of angiotensin II in the venous drainage of subcutaneous adipose tissue from obese patients, compared to lean subjects (Harte et al., 2005). This was the first direct evidence that adipose angiotensin II is released into circulation in humans and consequently may contribute to the association observed between obesity and hypertension.

In light of recent experimental data, the existence of a reciprocal cross-talk existing between the adipose organ and the adrenal gland has been suggested (Ronconi et al., 2008). Several studies have reported that some adipocyte-derived factors were able to directly stimulate aldosterone secretion by the adrenal glands (Goodfriend et al., 2004). Interestingly, such effect was dependent on the particular characteristics of adipocytes; in fact the secretagogue activity of adipocytes derived from obese hypertensive rats (SHRs) was significantly higher than that observed with adipocytes from normal weight rats. The contribution of adipocyte-derived factors directly stimulating aldosterone secretion by the adrenal gland could explain the enhanced aldosterone signaling observed in obese SHRs. These adipocyte-derived factors could directly stimulate aldosterone secretion by increasing the expression of steroidogenic acute regulatory peptide, 3β-hydroxysteroid dehydrogenase, and aldosterone synthase in the adrenal gland (Ehrhart-Bornstein et al., 2004; Nagase et al., 2006). Such effects were shown to be independent of adipocyte-derived leptin, IL-6, TNF-α, adiponectin, and also adipose angiotensin II secretion (Ehrhart-Bornstein et al., 2003). These findings suggest a direct involvement of adipose tissue in the development of arterial hypertension, through increased aldosterone release from the adrenal gland, which in turn will exacerbate increased blood pressure, endothelial dysfunction (Farquharson and Struthers, 2002) and inflammatory status (Caprio et al., 2008). On the other hand, increased levels of aldosterone secreted by adrenocortical cells, can bind and activate adipocyte MRs, which in turn induce adipose differentiation, expansion and inflammation (Fig. 1), hence sustaining the proposed regulatory loop between fat and adrenal (Fig. 2).

5. Clinical perspectives and potential therapeutic application of selective MR antagonists

Far from being a simple reservoir for nutrient storage, adipose tissue is now recognized as one of the central players in the integration and control of metabolic homeostasis and energy balance. Among other regulatory factors, adipose tissue is a target for steroid hormones, since adipocytes express GR, MR, androgen receptors (AR) and estrogen receptors (ER) (Turgeon et al., 2006). New and unexpected roles for adipose MRs have been recently characterized, which directly control adipocyte differentiation and expansion, pro-inflammatory capacity, insulin signaling and adipokine secretion. In addition, recent studies confirmed that excess mineralocorticoid activation is present in obesity and contributes to low-grade inflammation, insulin resistance and

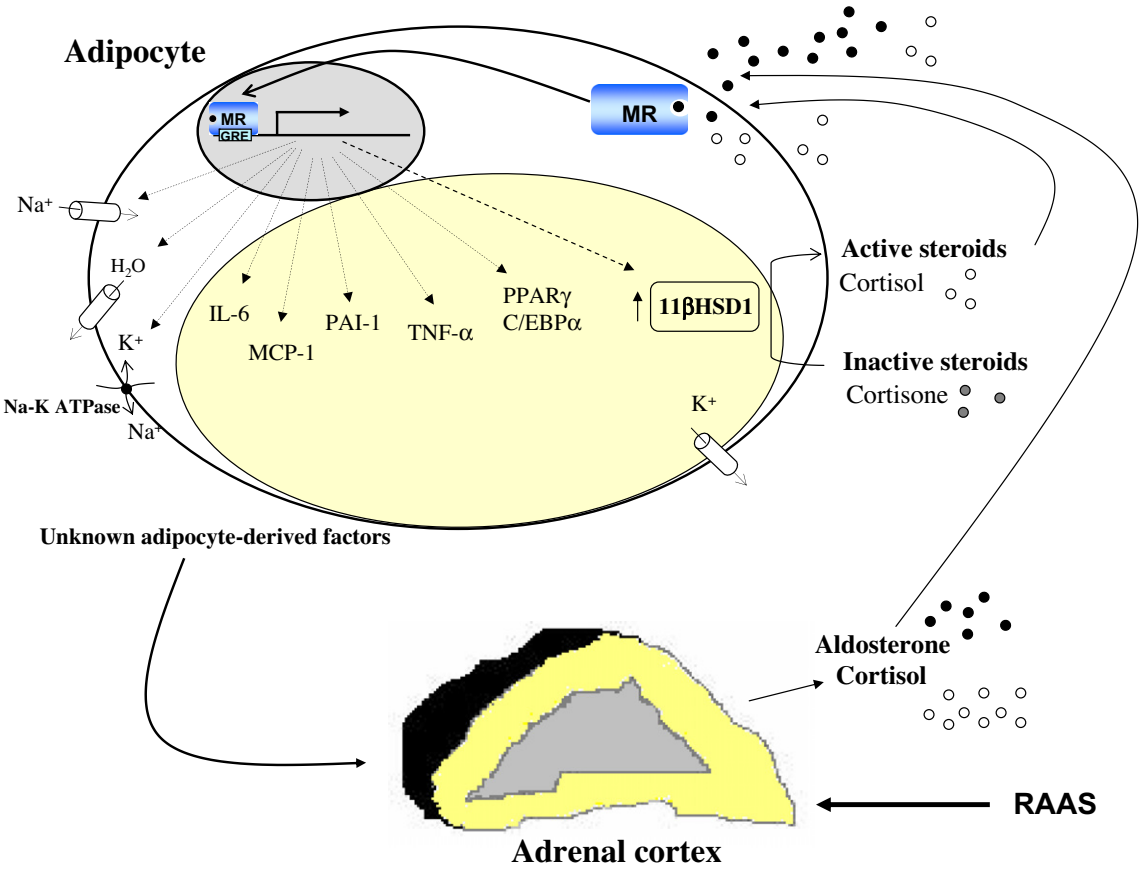

Fig. 2. Cross-talk between adipocyte and adrenocortical cell. Aldosterone (black) and cortisol (white) secreted by the adrenocortical cell, bind and activate adipocyte MR, which controls transcription of several target genes, such as PPARγ, C/EBPα, IL-6, MCP-1, PAI-1, TNF-α, involved in white adipocyte differentiation and inflammation. Moreover, MR activation up-regulates the expression of 11βHSD1, which amplifies local availability of glucocorticoids. On the other hand, unknown factors derived from adipocytes directly stimulate aldosterone secretion by the adrenal gland, in addition to the canonical control by RAAS activation.

cardiovascular injury (Guo et al., 2008; Hirata et al., 2009). This link between the mechanisms controlling adipocyte differentiation, energy balance, as well as salt homeostasis and blood pressure have placed the mineralocorticoid system as an attractive candidate for the development of obesity and its associated metabolic complications.

Even if studies in animal models of obesity showed a marked improvement of overall adipose tissue function after treatment with MR blockers (Guo et al., 2008; Hirata et al., 2009), to date, no clinical trials have addressed the impact of MR antagonism on body fat mass and adipose function as a primary end-point. Interesting indirect evidences has emerged from clinical studies of drospirenone, a potent synthetic anti-mineralocorticoid with progestogenic and moderate anti-androgenic properties, which is used in combination with estrogens for contraception and hormone replacement therapy (HRT) (Palacios et al., 2006). Drospirenone has been shown to display a positive impact on blood pressure (White et al., 2005, 2006; Preston et al., 2007) and body weight (Oelkers et al., 1995; Archer et al., 2005; Foidart and Faustmann, 2007); in particular a recent study in healthy postmenopausal women showed that it caused a significant decrease in central fat mass (Tanko and Christiansen, 2005). Based on these observations, we subsequently demonstrated a potent anti-adipogenic effect of the molecule on human primary preadipocytes from different fat depots, providing some mechanistic insights for the observed favorable effects of MR blockade on body weight and adipose tissue (Caprio et al., 2011).

Clinical studies of MR antagonists in selected cohorts of metabolically normal and abnormal obese patients should allow validation of this intriguing hypothesis.

6. Conclusions

The discovery of leptin completely changed the understanding of adipose biology, giving the adipocyte a new and unexpected role as major player in the context of the whole endocrine system. The ability to secrete many factors with a profound impact in metabolic homeostasis, together with the expression of a wide range of nuclear receptors, prompted researchers to investigate the critical pathways which become dysfunctional in human obesity. Adipose tissue dysfunction could potentially represent a primary metabolic trigger, providing the molecular basis for fat mass expansion, inflammation, and, as a direct consequence, insulin resistance and hypertension. MR is an intriguing molecular target which could explain the frequent association existing between the different components of the metabolic syndrome, since its over-activation has been proven to cause hypertension, endothelial inflammation, insulin resistance, and lately, altered function of adipose tissue.

The MR may hence represent a crucial element at the crossroads between blood pressure regulation and metabolic function, salt intake and diet. The development of specific modulators of MR signaling in adipocytes could open exciting new perspectives in the management of human obesity and metabolic syndrome.

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This work is dedicated to the memory of Rosellina Russo, and to my closest cousins.

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