

Adipocytes, aldosterone and obesity-related hypertension

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Abstract

Understanding the mechanisms linking obesity with hypertension is important in the current obesity epidemic as it may improve therapeutic interventions. Plasma aldosterone levels are positively correlated with body mass index and weight loss in obese patients is reported to be accompanied by decreased aldosterone levels. This suggests a relationship between adipose tissue and the production/secretion of aldosterone. Aldosterone is synthesized principally by the adrenal glands, but its production may be regulated by many factors, including factors secreted by adipocytes. In addition, studies have reported local synthesis of aldosterone in extra-adrenal tissues, including adipose tissue. Experimental studies have highlighted a role for adipocyte-secreted aldosterone in the pathogenesis of obesity-related cardiovascular complications via the mineralocorticoid receptor. This review focuses on how aldosterone secretion may be influenced by adipose tissue and the importance of these mechanisms in the context of obesity-related hypertension.

Key Words

- ▶ aldosterone
- ▶ synthesis
- ▶ adipocytes
- ▶ obesity-related hypertension

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Introduction

The obesity epidemic threatens to bring with it a significant range of health problems including the increased risk of hypertension and associated cardiovascular disorders. Of note, Brambilla and coworkers found that increased body mass index (BMI) was associated with treatment-resistant hypertension in a group of 1312 European patients with hypertension (Brambilla *et al.* 2013). Several mechanisms could underlie the development of hypertension in obesity, including direct pressure on the kidney, sympathetic nervous system activity and the over-activation of the renin–angiotensin–aldosterone system (Hall *et al.* 2015). In this study, we focus on the role of the mineralocorticoid hormone aldosterone in this system and the effects of manipulating this steroid hormone clinically and experimentally in obesity-related hypertension and metabolic conditions.

Emerging evidence implicates the aldosterone in the development of insulin resistance, metabolic syndrome and treatment-resistant hypertension (Vogt *et al.* 2007, Calhoun & Sharma 2010). Rising BMI has been shown to positively correlate with increasing plasma aldosterone levels in those with essential hypertension (Rossi *et al.* 2008) and similarly correlates with waist circumference and blood pressure (Grim *et al.* 2005, Bochud *et al.* 2006, Kidambi *et al.* 2007).

Synthesized in adrenocortical cells of the *zona glomerulosa*, aldosterone is a blood pressure-regulating hormone completing the well-described renin–angiotensin–aldosterone system (RAAS). Aldosterone exerts its physiological effects through the mineralocorticoid receptor (MR). MR is expressed in epithelial tissues such as the renal collecting duct, the colon and sweat glands,

where activation leads to insertion of transporters which increase sodium and water reabsorption. The receptor is also found in non-epithelial tissues such as the heart (Sainte-Marie *et al.* 2007), the vasculature (Nguyen Dinh Cat *et al.* 2010, McCurley *et al.* 2012) and adipose tissue (Caprio *et al.* 2007, Nguyen Dinh Cat *et al.* 2011, Briones *et al.* 2012). Interestingly, increased MR expression in adipose tissue has been observed in obesity (Hirata *et al.* 2012, Urbanet *et al.* 2015). Mice on a high-fat diet not only developed obesity, but also showed increased renal expression of MR protein and its downstream target serum- and glucocorticoid-regulated kinase-1 (SGK-1) (Tokuyama *et al.* 2012). MR binds both aldosterone and glucocorticoids with high affinity. However, glucocorticoids (cortisol for humans, corticosterone for rodents) circulate at 100- to 1000-fold higher concentrations than those of aldosterone (0.1–1 nM). In epithelial tissues, the enzyme 11beta-hydroxysteroid dehydrogenase type II (11b-HSD2) allows aldosterone to selectively activate MR, by converting cortisol to an inactive metabolite, cortisone (Edwards *et al.* 1988, Funder 2005, Marzolla *et al.* 2012).

Adipocytes can synthesize and secrete aldosterone which may exert autocrine and paracrine effects, influencing adipose tissue and local structures such as the

vasculature resulting in vascular remodelling (Nguyen Dinh Cat *et al.* 2011, Briones *et al.* 2012). In keeping with this effect on the vasculature, MR blockade has been shown to effectively reduce blood pressure in obesity-related hypertension, and the significant benefits in heart failure are well documented (Pitt *et al.* 1999, 2003).

Aldosterone production by adrenal glands

Classical regulators

Steroid biosynthesis occurs in the adrenal cortex from the precursor cholesterol. Cholesterol is initially converted to pregnenolone by the mitochondrial enzyme P450_{scc} (side chain cholesterol cleavage) encoded by the gene *CYP11A1*. The final step is catalyzed by two cytochrome P450 enzymes that display differences in their enzymatic activity, regulation and zonal distribution. 11β-hydroxylase (*CYP11B1*) synthesizes cortisol from 11-deoxyhydrocortisol (DOC) in the *zona fasciculata*, whereas the aldosterone synthase (*CYP11B2*) catalyses the conversion of DOC to aldosterone in the *zona glomerulosa* (Fig. 1A).

With aldosterone's role in the physiology and pathophysiology of the cardiovascular system, it is important to consider the regulation of its biosynthesis and secretion

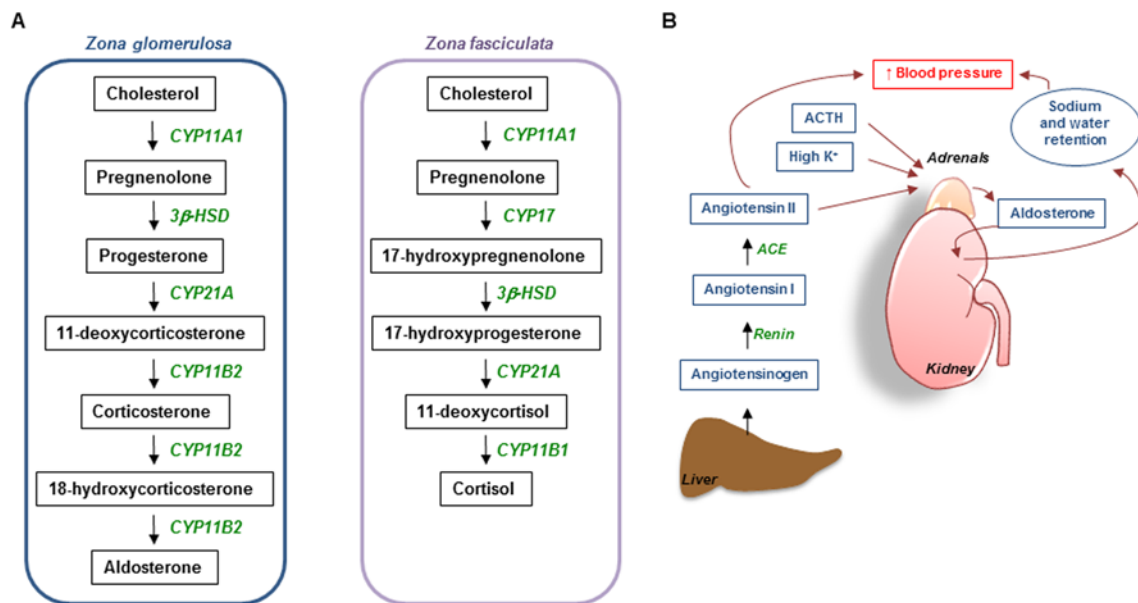


Figure 1

Synthesis of the mineralocorticoid hormone aldosterone and cortisol from cholesterol. Aldosterone is synthesized in the zona glomerulosa of the adrenal cortex by a series of enzyme steps leading to the conversion of cholesterol to aldosterone. There are two critical enzyme steps: (1) the conversion of cholesterol to pregnenolone cholesterol side-chain cleavage enzyme (*CYP11A1*) and (2) the conversion of corticosterone to aldosterone by the aldosterone synthase (*CYP11B2*). However, cortisol is synthesized in the zona fasciculata of the adrenal glands. *CYP11A1*, cholesterol side-chain cleavage enzyme (P450_{c11}); 3β-HSD, 3β-hydroxysteroid dehydrogenase; *CYP11B1*, 11β-hydroxylase (P450_{c11}); *CYP11B2*, aldosterone synthase. (B) Main regulators of aldosterone synthesis by the adrenals. A variety of factors modify the aldosterone secretion: the most important are the angiotensin II (AngII) and high concentrations of potassium (K⁺).

from the adrenal cortex, especially the signalling pathways involved in the secretory response to the controllers of aldosterone production (Fig. 1B) (Jaisser & Farman 2016). Angiotensin II (Ang II) and elevated serum potassium (K⁺) are the two main regulators of aldosterone production, whereas adrenocorticotrophic hormone (ACTH) and other proopiomelanocortin peptides, sodium, vasopressin, dopamine, atrial natriuretic peptide, beta-adrenergic agents, serotonin and somatostatin are minor modulators (Hattangady *et al.* 2012, Bollag 2014).

Treatment with Ang II or high levels of K⁺ results in a dose-dependent increase in aldosterone production by human adrenocortical H295R cells (Bird *et al.* 1993, Rainey *et al.* 1993). These agents have parallel effects on *CYP11B2* mRNA levels, whereas activation of the protein kinase A (PKA) pathway by cAMP analogues preferentially increases *CYP11B1* mRNA (Bird *et al.* 1995, Denner *et al.* 1996, Bassett *et al.* 2000). Ang II binds to G-protein-coupled receptors, activating phospholipase C which hydrolyzes PIP2 to IP3, increasing intracellular calcium (Ca²⁺) ions which activates Ca²⁺-calmodulin-dependent protein kinase (CaMK), and diacylglycerol-dependent protein kinase C (Hu *et al.* 2012, Felizola *et al.* 2014). ACTH, however, binds to the cell-surface melanocortin-2 receptor, which activates adenylate cyclase, produces cAMP and activates downstream PKA (Bassett *et al.* 2004). It is possible that these pathways have different efficiencies – perhaps the Ang II-mediated G-protein signalling pathway is simply better at increasing production of the necessary enzymes. The principle action of ACTH is in the *zona fasciculata* of the adrenal cortex where it stimulates the PKA-mediated phosphorylation of steroidogenic proteins, including the rate-limiting steroidogenic acute regulatory (STAR) protein (Arakane *et al.* 1997), which promotes the

transport of cholesterol into the mitochondria (Lin *et al.* 1995), where a number of enzymatic reactions lead to terminal glucocorticoid synthesis (cortisol in humans, corticosterone in rodents). By stimulating K⁺ excretion, aldosterone constitutes a negative feedback loop.

Adipocyte-derived factors

Approaches using adipose tissue-conditioned media to determine its effects on adrenocortical cell lines show increased steroidogenesis, both in murine and cellular models, following exposure to conditioned media (Ehrhart-Bornstein *et al.* 2003, Nagase *et al.* 2006, Krug *et al.* 2007). These studies suggest that the adipose tissue secretome contains ‘mineralocorticoid-releasing-factors’ that stimulate aldosterone synthesis in adrenocortical cells including aldosterone production which is increased in obese spontaneously hypertensive rats (Nagase *et al.* 2006). This further suggests a direct link with cardiovascular pathologies (Ehrhart-Bornstein *et al.* 2003, Krug & Ehrhart-Bornstein 2008).

Adipocyte-derived factors are proposed to mediate their effects through the canonical Wnt-signalling pathway (Schinner *et al.* 2007) and ERK1/2 mitogen-activated protein kinase (MAPK) signalling, resulting in increased STAR expression and sensitization to Ang II stimulus. However, this effect is not critically dependent on Angiotensin II via its receptor type 1 (AT₁R) (Krug *et al.* 2007). As adipocytes are also located within the adrenal glands, the factors they release may influence adrenals in a paracrine manner (Ehrhart-Bornstein *et al.* 2003). We describe three well-characterized adipocyte-derived factors that influence adrenal aldosterone secretion: leptin, adiponectin and complement-C1q TNF-related protein-1 (CTRP-1) (Fig. 2).

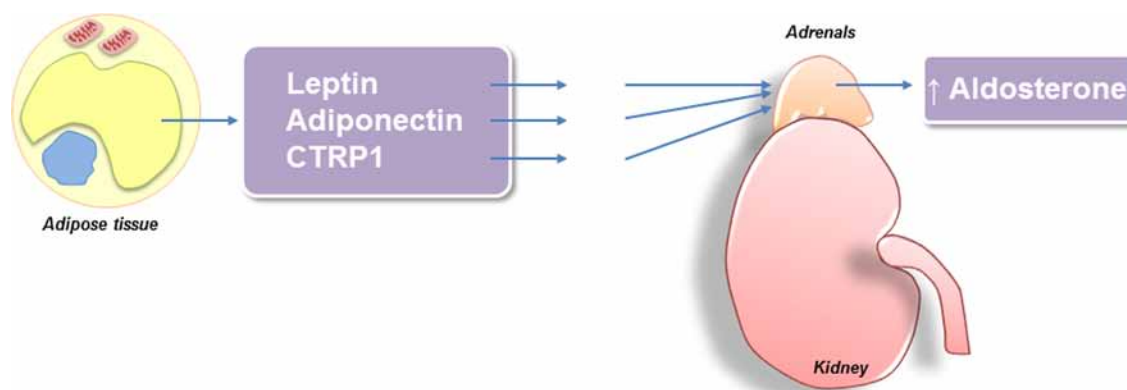


Figure 2 Novel regulators of aldosterone production in adrenals. New regulators of the secretion of aldosterone by the adrenal glands have been identified such as leptin, adiponectin and complement-C1q TNF-related protein-1 (CTRP1).

Leptin Leptin, known as the 'satiety hormone', is a 16kDa protein encoded by *Ob* gene and secreted mainly from white adipose tissue; it can be secreted in lower levels from other tissues, such as mammary gland, stomach, muscle, bone marrow, placental and fetal tissues (Friedman 2014, Park & Ahima 2015). Leptin receptors are highly expressed in the hypothalamus where they are required for the regulation of appetite, energy expenditure, body weight, thermogenesis, fertility and immune function (Ahima *et al.* 1996, Wada *et al.* 2014, Freitas Lima *et al.* 2015, Park *et al.* 2015). Downstream signalling in the central nervous system and peripheral tissues includes Janus-activated kinase/signal transducer and activator of transcription (Jak/STAT), insulin receptor substrate (IRS)/phosphatidylinositol 3 kinase (PI3K), SH2-containing protein tyrosine phosphatase 2 (SHP2)/MAPK and 5'-adenosine monophosphate-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC) (Yang *et al.* 2007, Park & Ahima 2014). Interestingly, serum leptin levels are significantly elevated in most obese individuals and correlate with BMI (Mantzoros 1999, Ahima 2008). Numerous investigations ranging from clinical and animal model studies to *in vitro* analyses implicate leptin in the pathogenesis of obesity-related cardiovascular diseases (Sweeney 2010, Hou & Luo 2011). Obese individuals can develop 'leptin resistance' where they become insensitive to the metabolic effects of leptin, but not to effects on the cardiovascular system (Pan *et al.* 2014, Balland & Cowley 2015, Sáinz *et al.* 2015). In a recent study, Huby and coworkers investigated whether leptin directly regulates aldosterone secretion by adrenals and whether this leptin-mediated aldosterone production impairs cardiovascular function (Huby *et al.* 2015). They showed that the leptin receptor and CYP11B2 are co-expressed in human and rats adrenal zona glomerulosa cells. They demonstrated that a) genetic reduction or increase in leptin signalling, respectively, prevents or enhances adrenal CYP11B2 expression and aldosterone release; b) endogenous and exogenous leptin directly activates CYP11B2, resulting in increased production of aldosterone via Ca²⁺-dependent mechanisms. This is independent of the renin-angiotensin and sympathetic nervous systems. Moreover, the authors demonstrated MR-dependent induction of endothelial dysfunction by leptin which was associated with increased levels of cardiac pro-fibrotic markers (Huby *et al.* 2015).

Adiponectin Adiponectin is a specific adipocyte-secreted protein that is metabolically active and anti-inflammatory (Sowers 2009, Nigro *et al.* 2014). Adiponectin can improve

insulin sensitivity and is inversely associated with obesity and insulin resistance, two common comorbidities in cardiovascular disease (Antoniades *et al.* 2009, Shibata *et al.* 2012, Nigro *et al.* 2014, Antonopoulos *et al.* 2015). Adiponectin receptors are present in human and mouse adrenal glands (Rossi *et al.* 2006, Li *et al.* 2009). In the murine adrenocortical Y1 cell line, adiponectin decreased steroidogenesis enzymes resulting in decreased aldosterone and corticosterone production (Li *et al.* 2009). However, in primary cultured rat adrenal cells, adiponectin increased steroidogenesis (Paschke *et al.* 2010). Additionally, in cultured human adrenocortical cells, adiponectin increased STAR expression and cortisol production, a process dependent on AMPK, Akt and ERK1/2 signalling. This may be an important regulatory system given that glucocorticoids are reported to decrease adiponectin secretion by adipocytes (Degawa-Yamauchi *et al.* 2005, Iwen *et al.* 2008). Levels of adiponectin are decreased in obese *db/db* mice and this is prevented by MR antagonism (Guo *et al.* 2008).

CTRP-1 Complement-C1q TNF-related protein-1 (CTRP-1) is an adiponectin paralogue with 30–50% shared sequence homology and may share some of adiponectin's biochemical properties. CTRP-1 is primarily and highly expressed from cells in the stromal vascular fraction of adipose tissue and is also specifically expressed in the zona glomerulosa of murine and human adrenal cortex and in vascular wall tissue (Wong *et al.* 2008). Jeon and coworkers demonstrated that CTRP-1 regulates adrenal aldosterone production through increases in intracellular Ca²⁺ levels and induction of CYP11B2 expression (Jeon *et al.* 2008). Moreover, CTRP1 did not increase the transcription of CYP11B1, the enzyme responsible for glucocorticoid synthesis. Previous reports found that Ang II increased the transcription of CYP11B1 and STAR (Li *et al.* 2003, Romero *et al.* 2004), and AT₁R blockade had no effect, suggesting that this aldosterone secretion induced by CTRP-1 is independent of Ang II-mediated regulation mechanism (Jeon *et al.* 2008).

Most data indicate that CTRP-1 is increased in obesity, although conflicting results exist. Kim and coworkers showed increased CTRP-1 levels in obese *db/db* mice and Zucker fatty rats (Kim *et al.* 2006). However, Peterson's group reported decreased levels of CTRP-1 in diet-induced obese mice, and that transgenic CTRP1 overexpressing mice are protected from obesity through increased AMPK activation and subsequent increased fatty acid oxidation and energy expenditure (Peterson *et al.* 2012). In addition, CTRP-1 levels were increased

in adiponectin-null mice (Peterson *et al.* 2012). Kim and coworkers reported a specific relationship between inflamed adipose tissue, stromal vascular fraction and CTRP-1, suggesting that the dysregulation of CTRP-1 levels in obesity is strongly associated with chronic inflammation in adipose tissue (Kim *et al.* 2006).

Additionally, patients with metabolic syndrome and type 2 diabetes have increased circulating levels of CTRP-1 compared with healthy individuals. This is positively correlated with BMI, fasting glucose, TNF- α (tumour necrosis factor- α) and HbA1c (glycated haemoglobin A1c) (Chalupova *et al.* 2013, Xin *et al.* 2014). Circulating levels of CTRP-1 are also increased in non-obese hypertensive patients; hence, CTRP-1 has been suggested as a critical protein associated with the pathophysiology of obesity-related hypertension (Jeon *et al.* 2008).

Non-adrenal production of aldosterone

Cardiovascular and central nervous systems

Extra-adrenal aldosterone production may represent important local regulatory mechanisms in tissues reliant on a dynamic vascular supply. In the cardiovascular system, the machinery for aldosterone production is found both in endothelial and smooth muscle cells (Takeda *et al.* 1995, Hatakeyama *et al.* 1996, Takeda *et al.* 1996). Transcripts of *Cyb11b2* are increased in aortas from spontaneously hypertensive rats (Wu *et al.* 1998), and isolated rat mesenteric arteries produce aldosterone (Takeda *et al.* 1995). Key steroidogenesis enzymes, including the terminal enzymes for corticosterone and aldosterone synthesis, are also expressed in the rat heart (Silvestre *et al.* 1998). Interestingly, aldosterone levels in the rat heart are approximately 17-fold higher than in plasma, possibly owing to a slower degradation rate (Delcayre & Silvestre 1999). In the central nervous system, neurosteroids were first established in 1987 when P450_{scc} was found to be expressed in white matter (Le Goascogne *et al.* 1987) and other cells of the brain including neurons and glial cells (Zwain & Yen 1999, Kushida & Tamura 2009). *Star* is highly expressed throughout the brain with maximal levels in the cerebellum (Furukawa *et al.* 1998), and both *Cyb11b1* and *Cyb11b2* are expressed in the brain (Strömstedt & Waterman 1995, Gomez-Sanchez *et al.* 1996, 1997).

Adipose tissue

Machinery for aldosterone synthesis and MR expression Included in the several hundred factors

produced by adipocytes are components of the renin-angiotensin system (Thatcher *et al.* 2009). Along with the expression of NR3C2 (MR) and NR3C1 (GR) in adipocytes (Caprio *et al.* 2007, 2011, Campbell *et al.* 2011), the necessary components for endogenous aldosterone production are present in rodent and human adipocytes (Nguyen Dinh Cat *et al.* 2011, Briones *et al.* 2012). Briones and coworkers demonstrated adipocyte secretion of aldosterone which was increased in obese animals and upon stimulation with Ang II. This adipocyte-derived aldosterone may in turn impact on adipocyte biology by regulating adipogenesis, but also on vascular function in an MR-dependent manner (Briones *et al.* 2012). Mechanisms of regulation of aldosterone production by adipocytes include both calcineurin/nuclear factor of activated T (NFAT) cells signalling pathways (Briones *et al.* 2012) and ROS-dependent pathways (Rios *et al.* 2015). Recently, the role of adipocyte-derived aldosterone was also implicated in renal disease. In fifth/sixth nephrectomized rats (a model of chronic renal failure) and in patients with chronic kidney disease (CKD), plasma levels of aldosterone and CYP11B2 expression in adipose tissue are increased, as well as MR nuclear expression and its downstream signalling targets (Hosoya *et al.* 2015). Treatment with MR antagonist spironolactone ameliorated insulin resistance in patients with CKD, and partially reversed impaired glucose tolerance in nephrectomized rats. It was suggested that adipocyte-derived aldosterone production may be contributing to the pathogenesis of insulin resistance in patients with CKD (Tirosch *et al.* 2010, Hosoya *et al.* 2015). In our studies, the ratio between adrenal- and adipocyte-derived aldosterone in mouse and humans for the levels of the aldosterone synthase is four times (Briones *et al.* 2012). Thus, the relative significance of this adipocyte-derived aldosterone compared with that of the zona glomerulosa remains an interesting question to elucidate. We demonstrated that this adipocyte aldosterone affects vascular signalling such as pro-fibrotic and pro-inflammatory signalling pathways (Nguyen Dinh Cat *et al.* 2011). Presumably, the actions of adipocyte aldosterone contribute to the effects of circulating levels of aldosterone.

Regulators of adipocyte aldosterone production

Ang II/calcineurin-NFAT Based on the work from Yamashiro and coworkers that reported regulation of CYP11B2 and aldosterone production via calcineurin-dependent pathway in adrenocortical cells (Yamashiro *et al.* 2010), Briones and coworkers also showed involvement of

this pathway in adipocyte-derived aldosterone. In differentiated 3T3-L1 adipocytes, Ang II/AT₁R regulates *Cyb11b2* expression and adipocyte-secreted aldosterone in a calcineurin/NFAT-dependent manner, an effect blocked by FAD286 (selective CYP11B2 inhibitor). Indeed, calcineurin inhibitors (cyclosporin A and FK506) and the specific NFAT inhibitor (VIVIT) abrogated Ang II-induced aldosterone secretion by adipocytes. In addition, Ang II stimulated NFAT nuclear translocation, an effect blocked by AT₁R blocker candesartan, and decreased NFATc4 phosphorylation, which was restored by cyclosporin A and FK506 (Briones *et al.* 2012) (Fig. 3A).

CETP inhibitors Cholesteryl ester-transfer protein (CETP) inhibitors increase the levels of high-density lipoprotein. Clinical trials of the CETP inhibitors torcetrapib (Barter *et al.* 2007) and dalcetrapib (Schwartz *et al.* 2012) revealed hyperaldosteronism and hypertension as clinically relevant adverse effects. Rios and coworkers showed that in a human adipocyte model, CETP inhibitors increased CYP11B2, CYP11B1 and STAR expression. In adipocytes,

this was associated with an increase in ROS generation and activation of peroxisome proliferation-activated receptor-gamma (PPAR-G) and signal transducer and activator of transcription 3 (STAT3) (Rios *et al.* 2015) (Fig. 3B). This regulation of aldosterone production in adipocytes sheds light on the close relationship between hypertension and hyperaldosteronism. The precise contribution of adipocyte-derived aldosterone remains to be determined; however, the adverse effects observed with CETP inhibitors infer a greater systemic role than currently accepted.

Reactive oxygen species Rajamohan and coworkers demonstrated that ROS are key regulators of aldosterone production in adrenal glands. In human and rat adrenocortical cells, Ang II increased ROS levels through upregulation of NADPH oxidase (Nox) 1, 2 and 4 and ultimately resulted in increased CYP11B2 levels and aldosterone production. Importantly, this process was blocked or attenuated by not only an AT₁R antagonist but also antioxidants, pharmacological Nox inhibition and siRNA-mediated Nox silencing. Similarly, exogenous

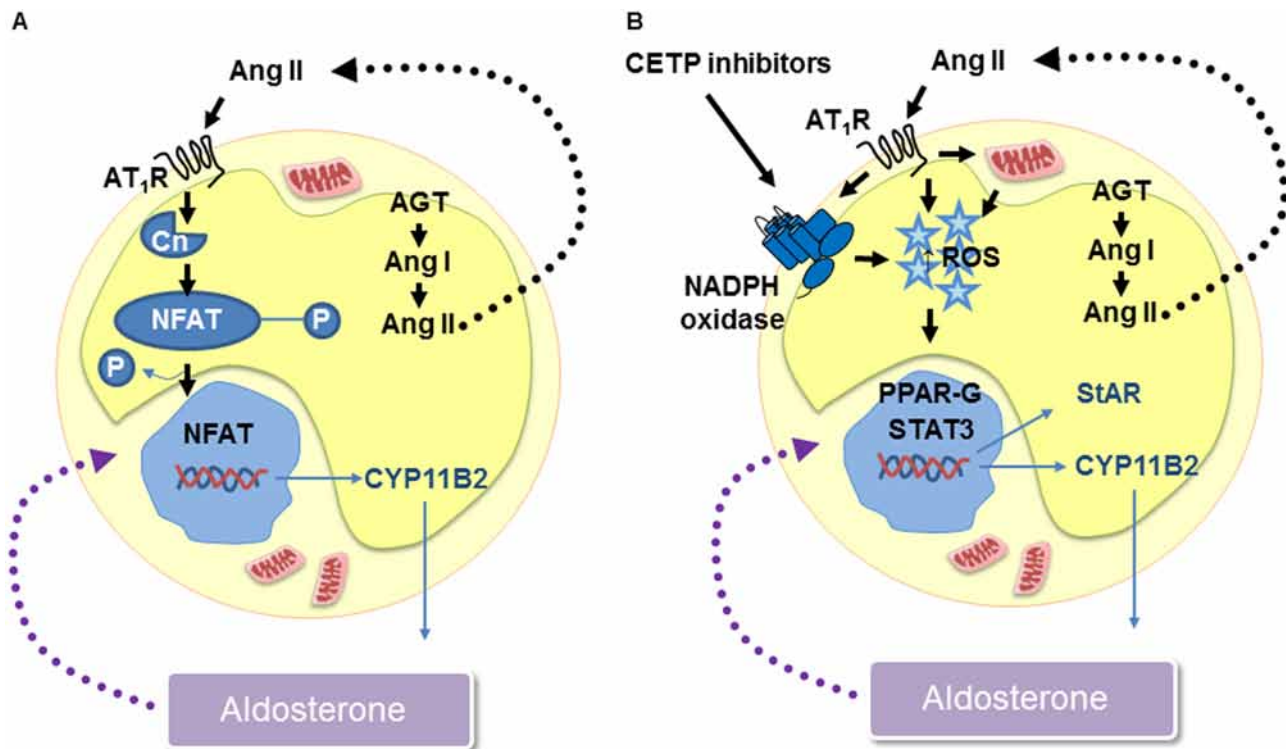


Figure 3 Regulation of aldosterone production in adipocytes. (A) Angiotensin II via its receptor type 1 (AT₁R) regulates the aldosterone synthase (CYP11B2) expression and the adipocyte-secreted aldosterone in a calcineurin/nuclear factor of activated T (NFAT)-dependent manner. (B) Cholesteryl ester-transfer protein (CETP) inhibitors regulates the aldosterone synthase (CYP11B2) expression through increase in ROS generation and activation of peroxisome proliferation-activated receptor-gamma (PPAR-G) and signal transducer and activator of transcription 3 (STAT3). AGT, angiotensinogen; Ang, angiotensin; ROS, reactive oxygen species; STAR, steroidogenic acute regulatory protein.

hydrogen peroxide can increase CYP11B2 activity, leading to increased aldosterone production by adrenocortical cells (Rajamohan *et al.* 2012). Several reports show increased ROS levels in adipose tissue from obese and/or hypertensive animals (Furukawa *et al.* 2004), raising the possibility of adipose tissue-derived ROS as the molecular connection between increased aldosterone levels and obesity-related hypertension. However, caloric restriction and exercise can improve the state of oxidative stress (Imayama *et al.* 2012). Nonetheless, a cause and effect relationship between oxidative stress and obesity is not well understood. Adipose tissue from obese *db/db* mice showed oxidative stress, increase in *Cyb11b2* expression, resulting in aldosterone production by mature adipocytes (unpublished observations). The Nox1/4-inhibiting compound GKT137831 decreased *Cyb11b2* mRNA levels and adipocyte-derived aldosterone production in obese *db/db* mice suggesting that oxidative stress does contribute to the pathogenesis of obesity.

AMPK activators In a published abstract, White and coworkers demonstrated that pharmacological activators of AMPK increase aldosterone secretion from cultured adipocyte models. In the murine adipocyte cell line 3T3-L1, the AMPK activator 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) increased aldosterone secretion into culture medium. Similarly, in the human adipocyte cell line SW872, the specific AMPK activator A769662 increased the aldosterone secretion along with STAR expression. However, when SW872 cells were treated with the diabetes drug and non-specific AMPK activator metformin, aldosterone secretion was not changed (White, personal communication). AMPK is a key energy regulator activated in low-energy states and is known to stimulate mitochondrial biosynthesis (Marcinko *et al.* 2014). Although the effect described here was initially unexpected, the author suggests it may be reasoned by a direct effect on mitochondrial number and therefore steroid production. Alternatively, this effect may represent a mechanism in the autoregulation of adipose tissue perfusion during starvation, when adipocyte-secreted vasoactive factors may be required without influencing systemic blood pressure. Considering that AMPK activity is reduced in adipose tissue of insulin-resistant obese patients undergoing bariatric surgery (Gauthier *et al.* 2011), it is likely that this mechanism may not be relevant in such individuals and therefore may represent a dynamic physiological rather than chronic pathophysiological regulation of

adipocyte aldosterone secretion. One study assessed the effect of AICAR on adrenal steroidogenesis focussing on androgen production. Here, AICAR activated AMPK in human adrenocortical cells (H295R) and increased the activity of CYP17A1-17,20 lyase to facilitate androgen production. The authors did not investigate the effects on aldosterone production (Hirsch *et al.* 2012). As discussed in the 'Adipocyte-derived factors' section adiponectin, which signals via AMPK, was found to have different effects on steroidogenesis in cultured adrenal cell lines from different species including increased STAR expression and cortisol secretion in H295R cells. In addition, adiponectin increased ACTH secretion from the mouse AtT20 pituitary cell line and rat primary pituitary cells, suggesting influence over steroidogenesis at different stages of the hypothalamic–pituitary–adrenal axis (Chen *et al.* 2014). It would be of interest to define the effect of adiponectin on adipocyte aldosterone production and to further examine the AMPK dependence of such effects.

Role of MR activation in adipose tissue Despite its key role in renal sodium reabsorption and blood pressure control, MR activation regulates important physiological functions in adipose tissue including differentiation of preadipocytes into mature adipocytes (Caprio *et al.* 2007, 2011) and promotion of adipose tissue inflammation via induction of cytokines (adipokines) including TNF- α , monocyte chemoattractant protein-1 (MCP-1) and IL-6 in white adipose tissue, while decreasing the thermogenic activity and lowering uncoupling protein-1 (UCP-1) transcription of brown adipose tissue (Zennaro *et al.* 2009, Kargi *et al.* 2014). Interestingly, MR mRNA expression positively correlates with increasing BMI in humans and is increased in obese *db/db* mice (Hirata *et al.* 2012, Urbanet *et al.* 2015). This suggests that MR over-activation in adipose tissue triggers deleterious effects within the adipose tissue; in particular, it contributes to insulin resistance and oxidative stress and to the development of obesity-associated cardiovascular complications (Sowers *et al.* 2009). Our group recently demonstrated that adipocyte-specific MR over-activation in mice leads to insulin resistance, visceral obesity and dyslipidaemia (Urbanet *et al.* 2015), as well as vascular dysfunction through redox-sensitive-dependent mechanisms (Nguyen Dinh Cat *et al.* 2016). Adipose tissues from these transgenic mice displayed increased levels of ROS, markers of macrophages and pro-inflammatory cytokines, including IL-6, MCP-1 and RANTES (regulated on

activation, normal T cell expressed and secreted) versus controls. In our conditional transgenic mouse model over-expressing MR in adipocytes, we do not know whether aldosterone or glucocorticoid activates MR in adipose tissue. This question remains under debate as reports showed that adipocytes do not have significant 11b-HSD2 activity and yet maintain a relatively high level of 11b-HSD1 activity, allowing glucocorticoids to be the main ligand for adipocyte-MR (Kargi *et al.* 2014). Moreover, visceral obesity and metabolic syndrome have been associated with increased adipose 11b-HSD1 activity, further increasing intra-adipocyte cortisol concentrations (Morton *et al.* 2004, Koska *et al.* 2006, Stimson & Walker 2007).

Aldosterone: clinical implications and targets

Obesity-related hypertension

Knowing that adipocytes can regulate both local adipose and adrenal aldosterone secretion, it is tempting to conclude that adipocytes are responsible for elevations in blood pressure in obesity. Primary hyperaldosteronism, due to either a unilateral adrenal adenoma or bilateral gland hyperplasia, is associated with insulin resistance in obese hypertensive patients (Catena *et al.* 2006, Garg *et al.* 2010), and such metabolic complications appear to be directly related to aldosterone as they are corrected by either adrenalectomy or MR antagonist. Aldosterone production is increased in normotensive overweight subjects and has a weak correlation with insulin resistance measured by homeostatic model assessment (HOMA-IR) (Bentley-Lewis *et al.* 2007). Obesity-associated inflammation contributes to the development of insulin resistance. Aldosterone has direct effects within adipose tissue including inducing insulin resistance and inflammation, again suggesting that aldosterone might be a link between obesity, insulin resistance and inflammation (Gilbert & Brown 2010, Tirosh *et al.* 2010, Bruder-Nascimento *et al.* 2014). Furthermore, in 3T3-L1 adipocytes, aldosterone was reported to degrade IRS-1 and IRS-2 via GR-mediated increased ROS which was associated with increased phosphorylation of nuclear factor kappa B (Wada *et al.* 2009). There is much interest in the mechanisms of aldosterone signalling in adipose tissue and it has been questioned whether there is an as yet undiscovered mechanism by which it mediates non-genomic effects (Nguyen Dinh Cat & Jaisser 2012).

As there is a wealth of evidence implicating aldosterone in the pathogenic mechanisms of obesity-related hypertension, it is of significant interest to consider the benefits of manipulation of this system and when this should be considered during the course of treatment.

Inhibitors of aldosterone synthesis and MR-activity

Spironolactone and eplerenone

Spironolactone Spironolactone is a non-selective MR antagonist which also antagonizes androgen and progesterone. In the UK, it is recommended for use in treatment-resistant hypertension, but is not licensed for this indication (NICE guidelines CG127 2011). It is used widely to treat heart failure and there is a wealth of evidence demonstrating its mortality benefits in this condition most notably from the landmark RALES study (Pitt *et al.* 1999). Unfortunately, it has some intolerable side effects due to the non-selective nature of its action, most frequently gynaecomastia which affected 10% of men in the RALES study (Pitt *et al.* 1999).

The potential benefits of spironolactone in metabolic conditions such as obesity-related hypertension are of interest and the literature to date is largely supportive of a beneficial role. In a group of obese hypertensive individuals treated with an ACE inhibitor with or without spironolactone, spironolactone was found to have greater benefits in blood pressure and urine albumin excretion (Bomback *et al.* 2009). Spironolactone improved LV function and decreased circulating pro-collagen levels in obese patients with impaired LV diastolic function (measured by mitral annular velocity) (Kosmala *et al.* 2013). Moreover, spironolactone may influence adipokine secretion such as adiponectin, which is normally decreased in obesity. In individuals with poorly controlled diabetes, spironolactone increased circulating levels of adiponectin but not in those with adequate glycaemic control (Matsumoto *et al.* 2006). Another study looking at the metabolic condition polycystic ovary syndrome found that spironolactone was beneficial in obese subjects who after 1 year had improved insulin sensitivity measured by homeostatic model assessment of insulin resistance (HOMA-IR) and decreased triglycerides (Zulian *et al.* 2005). Experimental studies have shown that MR, rather than the GR, is required for normal steroid-induced adipogenesis (Caprio *et al.* 2007). The same group has also shown that MR antagonism *in vivo* and *in vitro* can lead to browning of white adipocytes demonstrated by increased UCP-1 expression (Armani *et al.* 2014).

Eplerenone Eplerenone, a more selective MR antagonist, also benefits patients with heart failure (Zannad *et al.* 2011) and interestingly has additional benefits in those with diabetes following myocardial infarction compared with those without diabetes (O'Keefe *et al.* 2008). A substudy of the EMPHASIS trial examined diabetes risk, and found no difference in the incidence of type 2 diabetes in heart failure patients with or without eplerenone treatment (Preiss *et al.* 2012). In studies assessing endothelial function, eplerenone improved brachial artery flow-mediated dilatation in subjects with increased BMI (Hwang *et al.* 2013), and in C57BL/6 mice on high-fat diet, eplerenone attenuated impaired endothelium-dependent acetylcholine-induced vasorelaxation of aortic rings (Schäfer *et al.* 2013). Further evidence from preclinical studies supports a metabolic benefit of eplerenone. In a canine study, eplerenone attenuated high-fat-diet-induced increases in weight and blood pressure further implicating aldosterone or at least the MR in obesity-related hypertension (de Paula *et al.* 2004). Hirata and coworkers showed that eplerenone reduces insulin resistance and macrophage infiltration in adipose in *db/db* and *ob/ob* mouse models of obesity (Hirata *et al.* 2009).

However, in C57/Bl6 mice on a 60% high-fat diet for 20 weeks with or without eplerenone or adrenalectomy, serum aldosterone was highest in the group receiving eplerenone and was unaffected by high-fat diet alone. Eplerenone did not affect diet-induced weight gain or fatty liver but did prevent blood pressure elevation and attenuated diet-induced rises in serum insulin and HOMA-IR (Gamliel-Lazarovich *et al.* 2013). Another study that treated obese *db/db* mice from 8 to 25 weeks of age with eplerenone also showed no change in weight, but there was a prevention of pro-inflammatory gene expression in retroperitoneal adipose tissue (Guo *et al.* 2008).

Inhibitors of regulators of aldosterone

secretion Targeting the production of aldosterone to benefit cardiometabolic disorders associated with high-fat diet is intriguing given the benefits of MR antagonism. There is certainly evidence of increased circulating aldosterone in obese individuals, and this has been mimicked in rodents upon high-fat diet resulting in both increased circulating aldosterone and gene expression of *CYP11B2* in the adrenal glands (Northcott *et al.* 2012).

The metabolic functions of this enzyme have been interrogated using a transgenic aldosterone synthase knockout mouse model; these animals were less prone to

the elevated glucose, adipose tissue macrophage infiltration and hepatic steatosis associated with a 12-week high-fat diet. However, weight gain was unchanged and fasting insulin was highest in the aldosterone synthase knockout mice on the high-fat diet (Luo *et al.* 2013). This suggests involvement of aldosterone in some but not all of the adipose tissue dysfunction related to insulin resistance associated with obesity.

Driven by interest in this field, two novel drugs have been developed to inhibit aldosterone synthase, FAD286 and LCI699, which have been used in a number of studies evaluating their benefits. From a clinical perspective, these have ultimately been limited by the lack of specificity for aldosterone synthase (*CYP11B2*) compared with 11β -hydroxylase (*CYP11B1*). However, there is now evidence of benefit in Cushing's syndrome and clinical trials are ongoing in this area. Studies outlining the existing evidence of these agents have been thoroughly reviewed by Hargovan and Ferro (Hargovan & Ferro 2014).

Preclinical studies of FAD286 have focused on hypertension and heart failure models. For example, FAD286 was found to significantly inhibit the renin-angiotensin-aldosterone system-mediated cardiac fibrosis and hypertension in a transgenic mouse model overexpressing human renin and angiotensinogen, although to a lesser extent than the AT_1R blocker, losartan (Fiebeler *et al.* 2005). In addition, spontaneous hypertensive rats treated with FAD286 and spironolactone displayed severe dehydration and hyperkalaemia (Menard & Pascoe 2006). Another feature of aldosterone synthase inhibition is the increase of precursors such as deoxyhydrocorticosterone/deoxyhydrocortisol (DOC) which may have independent clinical effects.

Although designed to be more aldosterone synthase-specific than FAD286, LCI699 was also shown to alter cortisol synthesis and hypothalamic-pituitary-adrenal function. Despite this, a number of trials have been published relating to aldosterone dynamics including phase 1 and 2 studies which found a significant reduction in circulating aldosterone (Amar *et al.* 2010, Rossignol *et al.* 2011). Additionally, LCI699 has been compared with eplerenone in blood pressure regulation in two studies; one showed similar blood pressure improvements compared with eplerenone (Calhoun *et al.* 2011), whereas the other showed no blood pressure reduction despite lowering aldosterone levels (Karns *et al.* 2013).

It must be recognized that aldosterone is not the only ligand for MR and cortisol may mediate a proportion of the metabolic effects mediated via MR, particularly in adipose

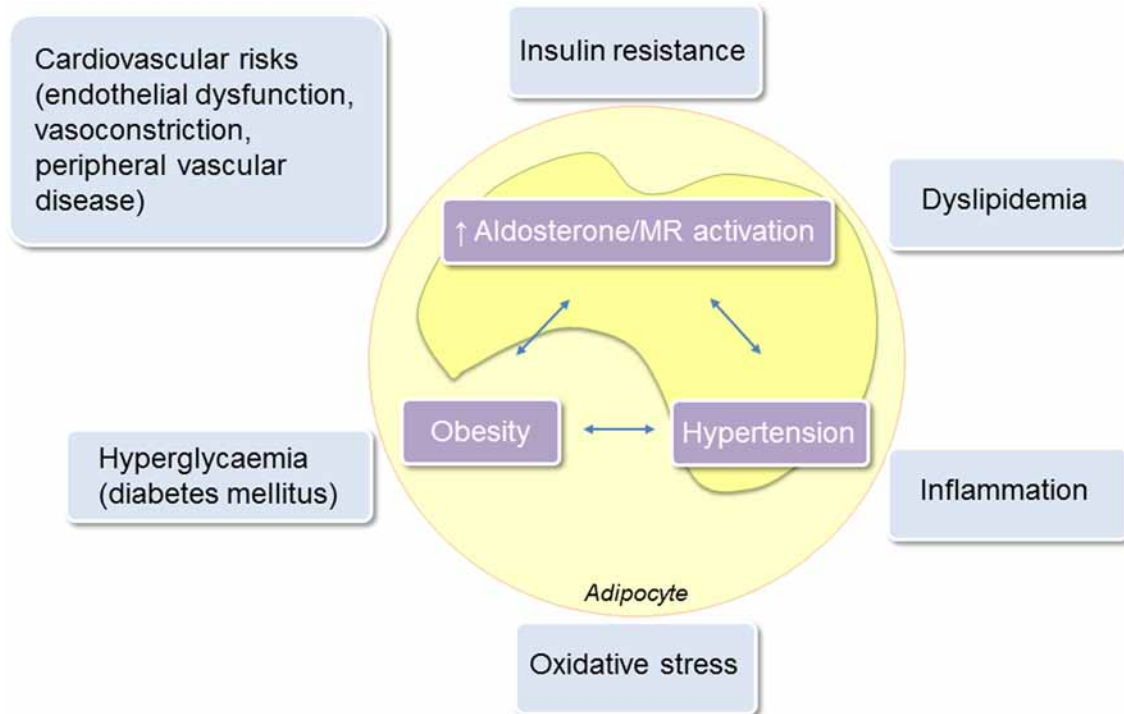


Figure 4 Summary of the pathophysiological roles of adipose aldosterone/MR activation in obesity-related hypertension.

tissue which lacks the cortisol converting enzyme 11-beta hydroxysteroid dehydrogenase. Indeed, recent evidence demonstrates that cortisol is co-secreted in around 10% of cases of primary hyperaldosteronism (Spath *et al.* 2011, Fujimoto *et al.* 2013).

Modulation of adipokines Knowing that adipokines can modulate aldosterone secretion, we consider that modulation of adipokines, through weight loss, exercise or medication, may be directly responsible for decreasing aldosterone and perhaps this is an area for therapeutic manipulation. If we consider leptin, which has been shown to increase aldosterone secretion, it may be that this is an important mechanism in obesity-related hypertension. However, this concept is complicated by the common coexistence of leptin resistance in obesity (Crujeiras *et al.* 2015) and that in the *db/db* mouse model, where there is a point mutation of the leptin receptor, aldosterone levels are elevated (Briones *et al.* 2012). Inhibiting leptin would therefore not seem a viable target for the manipulation of this system. Further identification of possible targets or adipokines involved in aldosterone secretion would therefore be useful.

Summary and conclusion

Understanding the mechanisms linking obesity with hypertension is important in the current obesity and hypertension epidemic and might have implications for the management of hypertension in overweight and obese patients. We have outlined some mechanisms whereby adipocytes may influence tissue and systemic aldosterone levels and suggest this as an important new mechanism linking obesity and hypertension. Figure 4 summarizes the pathophysiological roles of adipose aldosterone/MR activation in obesity-related hypertension.

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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