Review

Adipose tissue renin–angiotensin–aldosterone system (RAAS) and progression of insulin resistance

Yonit Marcus [a,1], Gabi Shefer [a,b,1], Naftali Stern [a,c,*]

[a] Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel
[b] Department of Biological Structure, University of Washington School of Medicine, Seattle, Washington, USA
[c] Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

ARTICLE INFO

ABSTRACT

This review focuses on the expression of the key components of the renin–angiotensin–aldosterone axis in fat tissue. At the center of this report is the role of RAAS in normal and excessive fat mass enlargement, the leading etiology of insulin resistance. Understanding the expression and regulation of RAAS components in various fat depots allows insight not only into the processes by which these complex patterns are modified by the enlargement of adipose tissue, but also into their impact on local and systemic response to insulin.

Contents

---

* Corresponding author. Address: Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel. Tel./fax: +972 36974578.
   E-mail address: stern@tasmc.health.gov.il (N. Stern).
[1] First two authors contributed equally to this manuscript.

1. Introduction: Basic components of the renin–angiotensin–aldosterone system (RAAS)

The classical systemic RAAS generates hormones that are key regulators of blood pressure, fluid and electrolyte balance and play a role in the pathogenesis of cardiovascular diseases. Renin is a proteolytic enzyme that is produced in the juxtaglomerular (JG) apparatus in the kidney and its secretion is stimulated mainly by (a) reduced renal perfusion pressure, hypotension, that translate into (b) low NaCl levels in the distal tubules of the kidney; and (c) increased sympathetic activity (sensed by β_1-adrenoceptors located on the JG). There is evidence that prostaglandins (PGE_2 and PGI_2) stimulate renin release in response to reduced NaCl levels in the kidney. When renin is released to the circulation it metabolizes its only substrate, angiotensinogen (AGT), which is primarily synthesized in and released from the liver to the blood stream. The action of renin on AGT results in the production of a decapeptide, angiotensin I (Ang I). Mostly in pulmonary circulation, Ang I is converted into the octapeptide Ang II by the angiotensin converting enzyme type 1 (ACE1 or ACE) which is nearly ubiquitously bound to vascular endothelial cells. ACE also inactivates the potent vasodilators bradykinin and kallidin (Carey and Siragy 2003). Taken together, the succession of enzymatic actions of renin and ACE result in increased vasoconstriction and decreased vasodilation. The most important and well studied effects of Ang II are mediated by two distinct G-protein-coupled receptors, AT1 and AT2. Ang II elicits an *increase in blood pressure* and blood volume by: (a) stimulating vasoconstriction through interaction with AT1 receptors (AT1R) located in vascular smooth muscle cells of the arterial wall; (b) *sodium retention*, both directly by increasing sodium (Na) reabsorbtion in the renal proximal tubules via AT1R and indirectly, via activation of AT1R in the adrenal zona glomerulosa (Aguilar et al., 2004). AT1R activation in the adrenal glands induces the synthesis and secretion of aldosterone that enhances sodium and water retention, increases potassium (K) excretion and increases blood pressure. Ang II itself via the interaction with AT2R mediates some "counter effects", including subtle vasodilator and anti-proliferative effects.

In addition to this dominant effector arm of RAAS, comprised mainly of ACE, Ang II, and AT1R as the mediator for the biological actions of Ang II, a functionally opposing arm has been more recently appreciated. In this branch, angiotensin–converting enzyme 2 (ACE2) is a key enzyme which generates Ang 1–7 by hydrolysis of Ang II. The Mas receptor then mediates "counter effects" of Ang 1–7 such as vasodilatation, inhibition of proliferation and anti-fibrosis (Santos et al., 2003).

2. RAAS components are locally expressed in white adipose tissue

2.1. Angiotensinogen, renin, Ang II forming enzymes, Ang II and Ang II receptors

There is evidence for mRNA expression of all, and protein expression of some, of the components essential for a complete local RAAS in adipocytes of the white adipose tissue (WAT). Specifically, the gene that encodes renin was found to be expressed in adipose tissue, which also expresses Cathepsin D and G, enzymes that can produce Ang I and Ang II, respectively, through RAAS alternative routes (Karlsson et al., 1998). There is evidence that cell membrane associated renin- receptors are present in human adipose tissue, predominantly in the stromal vascular fraction. Further, renin receptor expression was higher in visceral than in subcutaneous adipose tissue of both lean and obese human subjects (Achard et al., 2007). Post-natal high-fat diet in rats resulted in an increased fraction of pro-renin receptor expressing cells in adipose tissue. Moreover, a positive relationship was seen between plasma renin activity and the density of pro-renin receptor expressing cells (Achard et al., 2011). Renin and pro-renin binding to renin-receptors evokes enhanced renin enzymatic activity that results in increased Ang II formation and also independently activates intracellular signaling which mediates the expression of fibrotic proteins (Nguyen 2011). Thus, food-induced increased expression of the renin-receptor in fat could lead to increased local RAAS activity, overproduction of Ang II that may leak out of WAT to the circulation and increase systemic levels of Ang II. Elevated levels of Ang II exert unwanted effects on blood pressure.

Rodent and human adipose tissues express the AGT gene and protein (Cassis et al., 1988; Jones et al., 1997; Karlsson et al., 1998). There is a strong association between the expression of adipose AGT gene and blood pressure. Targeted expression of AGT in adipocytes of wild type and AGT-knockout mice resulted in elevated blood pressure. In the same vein, mice that do not express AGT exclusively in their WAT have reduced plasma AGT levels and lower systolic blood pressures compared with controls (Massiera, et al. 2001a). These data attest for the contribution of adipocyte-derived AGT to the systemic RAAS and the control of blood pressure (Yiannikouris et al., 2012). Additionally, adipocyte specific targeted overexpression of an enzyme that generates active cortisol (11β-hydroxysteroid dehydrogenase-1) induced elevated blood pressure in association with high plasma AGT and adipose tissue AGT gene expression in mice (Masuzaki et al., 2003). This could have resulted, at least in part, from cortisol-dependent induction of adipose-AGT expression. Other components of the RAAS system such as the ACE and ACE2 genes, and Ang II receptors (predominantly AT1R), at the protein level, were also detected in adipose tissue (Gupte et al., 2008; Jonsson et al., 1994; Crandall et al., 1994). AT1R is nearly ubiquitously expressed, and AT2R expression is generally low and restricted to just a handful of tissues in adults. AT2R expression levels were reported to increase during adipocyte differentiation (Mallow et al., 2000). In fact, both adipocytes and preadipocytes express not only AT1R and AT2R, but also the less well recognized receptors for Ang IV and Ang 1–7 (MasR; Weiland and Verspohl 2008).

An interesting question is whether the local adipose tissue RAAS is totally or partially independent of systemic RAAS, as reflected in its circulating effector hormones. A study in rats showed that WAT renin was independent of plasma renin levels, exclusive of extremely high levels. This is unlike the heart, where the expression

of cardiac tissue and plasma renin were positively correlated. Moreover, in rodents, adipocyte-derived AGT comprised about 30% of the circulating AGT levels (Cassis et al., 2008; Faloia et al., 2002; Massiera et al., 2001a). The local adipose RAAS appears, therefore, to function independently of plasma RAAS via independent control of renin levels but influences circulatory RAAS (Fowler et al., 2009b). This complex relationship is especially intriguing considering that excess body fat, particularly in the visceral depot, is closely related to hypertension and the dysmetabolic state. Likewise, the ability of adipose cells to produce and secrete Ang II may explain, at least partially, the deterioration of typically non-fatty organs which become the target of ectopic fat deposition once fat storage capacity in adipose tissue is exceeded. The best known examples for such ectopic fat infiltration are visceral organs such as the liver, pancreas and kidneys, as well as myocardial, perivascular and skeletal muscle fat deposition. Fat accumulates in these tissues either as an adipose tissue capsule or as a fibrous cover containing adipocytes.

2.2. ACE2, Ang 1–7/MAS and adipose tissue

ACE2 (mRNA and protein) is expressed in adipose tissue (Gembardt et al., 2005), but its physiological role is not as well understood. Several mechanisms for ACE2 actions were suggested, including differential glycosylation, shedding from the cell membrane and tissue-specific regulation through inhibition of Ang II synthesis or activity (Ferrario et al., 2005; Lambert et al., 2005). Recent studies demonstrate that ADAM17, the metallopeptidase that cleaves TNF-α from cell membranes, can also mediate the shedding of ACE2 (Lambert et al. 2005). Increased ADAM17-dependent shedding of TNF-α has been implicated as a link between obesity and T2D, albeit the role of ADAM17-mediated ACE2 shedding in diseases that are associated with activated RAAS has not been established. Recently, Gupte et al. (2008) reported that short-term high fat diet increased ACE2 expression in adipose tissue whereas chronic fat rich diet continued to promote ACE2 mRNA expression but did not increase ACE2 protein or enzymatic activity. The shedding of ACE2 from adipocyte cell membranes may down regulate local Ang II concentrations and thus affect adipose tissue remodeling. ACE2 shedding from adipocytes may also explain discrepancies between ACE2 mRNA expression and protein abundance/activity as reflected by the finding that despite an increase in ACE2 mRNA upon high fat diet, systemic RAAS was actually activated. Not only can adipose ACE2 reduce local Ang II concentration, but in primary cultured mouse epididymal adipocytes, Ang 1–7 (the product of ACE2) was shown to reduce ROS formation and NADPH oxidase mRNA levels and increase basal and insulin-stimulated glucose uptake, possibly through induction of adiponectin expression (Liu, et al., 2011).

Downstream to ACE2, interference with the Mas receptor integrity resulted in disruption of normal adipose tissue function: Mas-knockout (Mas-KO) mice developed ∼50% increase in abdominal fat mass associated with reduced insulin sensitivity hyperinsulinemia, hyperleptinemisa, hypercholesterolemia and hypertriglyceridemia. Decreased GLUT4 in adipose tissue along with increased expression of TGFβ and AGT genes was also seen in Mas-KO animals (Santos et al., 2008).

2.3. Aldosterone interactions with adipose tissue

Human adipocytes produce an as yet uncharacterized mineralocorticoid-releasing factor which stimulates adrenal aldosterone production (Lamounier-Zepter and Ehrhart-Bornstein, 2006). One candidate compound which could link obesity to increased circulating aldosterone is an epoxy-keto derivative of linoleic acid. This substance is a potent stimulator of aldosterone production and is present in obese persons with increased levels of free fatty acids (FFAs). Increased oxidative stress could drive the production of this aldosterone-stimulating FFA oxidation product (Goodfriend et al., 2004). Consistent with this is the finding that the aldosterone secretagogue activity of adipocyte–conditioned medium from obese spontaneously hypertensive rats (SHR) was significantly zgreater than that from nonobese SHRs (Nagase et al., 2006). Very low-density lipoproteins (VLDL) comprises another potential link between dysmetabolic obesity and increased aldosterone levels as VLDL was shown to directly enhance aldosterone synthesis in- and secretion from-human and bovine adrenal cells and in the adrenocortical cell line H295R, largely via induction of the protein expression of steroidogenic acute regulatory (StAR) and aldosterone synthase (CYP11B2) (Xing et al., 2012). Additionally, weight reduction (that results in reduced VLDL levels) decreases plasma aldosterone levels and improves insulin sensitivity in both normotensive and hypertensive patients (Dall'Asta et al., 2009; Tuck et al., 1981).

In rodent adipose tissue, aldosterone and mineralocorticoid receptor activation increase proinflammatory adipokine expression, that in turn results in reduced insulin receptor expression and impaired insulin-induced glucose uptake (Ehrhart-Bornstein et al., 2004; Rondinone et al., 1993). Indeed, adipocytes from the subcutaneous adipose tissue of a patient with primary aldosteronism (PA) had lower mRNA and protein expression of insulin receptors (IR) (Carranza et al., 1991). Interference of aldosterone with insulin's action may underlie the increased rate of the metabolic syndrome and aberrant glucose metabolism in PA reported in some, but not all, studies (Fallo et al., 2006; Giacchetti et al., 2007; Matrozova et al., 2009). Increased levels of circulating resistin, another adipose tissue derived inducer of insulin resistance, were also reported in subjects with PA (Iacobellis et al., 2010). Caprio et al. showed that aldosterone, acting via mineralocorticoid receptors (MR), accelerated adipose conversion of 3T3-L1 cells and differentiation of 3T3-F442A cells in a time- and dose-dependent manner. MR, but not glucocorticoid receptor knockdown inhibited glucocorticoid-stimulated adipose conversion of 3T3-L1 cells (Caprio et al., 2007; Guo et al., 2008). Finally, studies in obese diabetic mice have demonstrated that MR blockade reduced adipocyte size and lowered the expression of proinflammatory and prothrombotic factors in adipose tissue, along with increased expression of adiponectin, thus potentially reversing fat-tissue excess induced adipocye dysfunction (Guo et al., 2008).

MR activation apparently plays a complex role also in brown adipocyte differentiation and function. In a cell line of rodent brown preadipocytes (T37i) aldosterone accelerated triglyceride accumulation, along with increased expression of adipogenic genes such as lipoprotein lipase (LPL), peroxisome proliferator- activated receptor γ (PPARγ) and adipocyte-specific fatty acid binding protein (aP2) but prevented the expression and function of brown-fat specific uncoupling protein–1 (UCP–1). These results indicate that MR activation may not only promote brown adipocyte differentiation but also block thermogenesis (reviewed in (Marzolla et al., 2012). MR activation may be critical also for white adipose cell differentiation (Caprio et al., 2011), however this effect is probably exerted *in vivo* by cortisol rather than aldosterone, considering the large excess of cortisol over aldosterone in WAT, along with the lack of the cortisol-neutralizing enzyme 11β hydroxysteroid dehydrogenase type 2 in white adipocytes.

2.4. The effects of RAAS on the different body fat depots

The health risk of overweight depends, to a large extent, on the particular distribution pattern of excessive adipose tissue. In the late 50s, the terms "android" and "gynoid" obesity were used to describe upper-body and lower-body adiposity, respectively

(Vague, 1956). More accurately defined, body fat may be stored in the following compartments:

- Subcutaneous adipose tissue – beneath the surface of the skin
- Visceral/central adipose tissue – inside the peritoneal cavity, on the visceral tree and between the internal organs and torso
- Lower body/gluteo-femoral region adipose tissue – hips, posterior pelvic region and thighs
- Ectopic/Non-adipose intra-abdominal solid organs – liver, pancreas, kidney, skeletal muscle, the heart and the perivascular space.

Subcutaneous fat is the largest adipose depot in humans, yet visceral fat, which makes up only about 20% of total fat, exerts a more potent metabolic effect and is strongly associated with obesity-related complications such as type 2 diabetes (T2D) and coronary artery disease (Hamdy et al., 2006). Three likely explanations underlie this increased negative influence of visceral fat, which far exceeds its relative actual size: (1) its intra-abdominal location, allowing direct drainage of its products to the portal circulation, leading to disproportionately increased effects on the liver and its metabolic machinery; (2) enhanced lipolytic activity of intra-abdominal adipocytes, allowing access to the liver of high concentrations of released FFAs (Bays et al., 2007; Bergman and Mittelman, 1998); (3) increased output of proinflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) and decreased adiponectin production in visceral adipose tissue in association with an apparently more abundant and inflammation-prone population of resident macrophages (Yokota et al., 2000).

In this unique environment, visceral adipose tissue also exhibits significantly elevated AGT mRNA compared with subcutaneous adipose tissue (Giacchetti et al., 2002). In patients with the metabolic syndrome, blockade of the AT1 receptor by telmisartan decreased visceral and not subcutaneous fat area after 24 weeks of treatment (Shimabukuro et al., 2007), thus suggesting that local Ang II production by visceral adipocytes may act in a paracrine manner to further facilitate adipose growth and proliferation.

Unlike other fat depots, the gluteofemoral fat apparently possesses protective properties in subjects with a wide range of age, BMI and co-morbidities. Specifically, gluteofemoral fat is associated with lower total cholesterol, low-density lipoprotein (LDL) cholesterol, VLDL and higher high-density lipoprotein-cholesterol (HDL) levels (Ozbey et al., 2002; Seidell et al., 2001; Williams et al., 1997; Yim et al., 2008). The mechanisms underlying these striking features of gluteofemoral adipose tissue remain obscure, but could be related to differential regulation of upper- and lower-body fat in terms of lipolysis, fatty acid uptake and inflammation. Bluntly phrased, upper/visceral fat may be more easily evoked by excess fat storage to put out a large flow of metabolic disruptors such as fatty acids per se, inflammatory cytokines, chemoattractants, eicosanoids and fat-derived hormones, whereas the lower body fat may act as a "fat cushion", absorbing fat and fat-derived disruptors with only a limited negative metabolic response. Poorer RAAS expression in the gluteofemoral could be one component of such more metabolically quiescent fat, although this remains entirely conjectural at the present time.

Studies suggest that ectopic fat is metabolically active and exerts both positive and negative effects on intimately neighboring organ (Cassis et al., 2008; Szasz and Webb 2012). For example, periaortic adipose tissue was shown to increase vascular smooth muscle contractile responses to some perturbations, such as electrical stimulation (Lu et al., 2010; Soltis and Cassis 1991). Conversely, in transgenic mice that lacked periaortic adipose tissue, blood pressure was elevated (Lee et al., 2009; Takemori et al., 2007). Accumulation of lipids occurs also in the skeletal muscle tissue

and interferes with insulin action and results in insulin resistance (Pan et al., 1997). The contribution of RAAS to this process was exemplified in experiments demonstrating that intramuscular lipid content in fructose fed rats was reduced by RAAS blockade with either AT1R blocker or ACE inhibitor (Furuhashi et al., 2004).

3. Regulation of fat RAAS

Nutrition and aging are key factors that regulate adipose local RAAS. Human and animal models demonstrated that systemic RAAS activity positively correlated with body weight and more specifically with body fat, and that weight loss associated with decreased RAAS activity both systemically and locally in WAT (Boustany et al., 2004; Engeli et al., 2005; Rahmouni et al., 2004; Tuck et al., 1981). ACE2 is also nutritionally regulated. For example it was shown that high-fat diet induced increased ACE2 expression and activity (Gupte et al., 2008). Signaling molecules implicated in the regulation of AGT expression in the liver and other tissues have been assessed for their potential role in adipocytes include glucocorticoids, androgens, cAMP, Ang II and insulin (Aubert et al., 1997, 1998; McGehee et al., 1993; Serazin-Leroy et al., 2000).

3.1. Nutrition

Overnutrition regulates the development of abdominal adipose tissue and RAAS components, regardless of the phase in life in which excessive feeding occurs. Specifically, the in vivo expression of AGT in adipose tissue was reduced by fasting and markedly increased by re-feeding (Frederich et al., 1992; Yasue et al., 2010). Feeding-related changes in the adipocyte expression of AGT were shown to be accompanied by parallel changes in blood pressure (Boustany et al., 2004; Frederich et al., 1992) and were most notably independent of plasma and hepatic AGT levels, which did not change (Frederich et al., 1992). Increased local formation of Ang II in adipose tissue has been originally observed in genetically or diet-induced obese rodents and in obese humans (Frederich et al., 1992; Hainault et al., 2002; van Harmelen et al., 2000). Post-natal overnutrition plays a role the development of visceral adipose tissue and apparently in the subsequent evolution of metabolic dysregulation in adulthood. In rats, both post-natal overfeeding and high-fat diet were shown to induce increased immunoreactivity for (pro)renin receptor in fat tissue stromal cells (Achard et al., 2011).

In adults, biopsies taken from healthy men at the beginning and after 2 weeks and 2 months of over-feeding showed that the early adaptive response to weight gain associated with enhanced expression of a number of RAAS components, including proteases that specifically produce angiotensin-related peptides, such as ACE, membrane metallo-endopeptidase (MME), mast cell protease (CMA1), cathepsin G (CTSG) and glutamyl aminopeptidase (ENPEP). This coordinated regulation strongly suggests an increase of angiotensin activity in human adipose tissue during weight gain (Alligier et al., 2012). In contrast, weight loss or fasting leads to a decrease in fat and plasma AGT (de Kloet et al., 2010; Yasue et al., 2010).

Not only the amount but also the type of nutrition (e.g., high fat, carbohydrates or high salt) affects RAAS. Activation of RAAS occurred in response to 10–11 weeks of high-fat diet in rodents, with a marked increase in plasma concentration of Ang II (Benson et al., 2004; Boustany et al., 2004). Decreased ability to accumulate body fat was seen in RAAS deficient animals such as the AGT-deficient (Agt$^{-/-}$) mice (Massiera et al., 2001a), renin Ren2c ($^{-/-}$) mice (Takahashi et al., 2007), AT1R- and AT2R-deficient mice (Kouyama et al., 2005; Yvan-Charvet et al., 2005) or in animals receiving AT1R

blockers (Araki et al., 2006). The ACE inhibitor captopril reduced the synthesis of adipose Ang II and also decreased leptin synthesis and release (Cassis et al., 2004). In the same vein, the renin inhibitor aliskiren reduced adipose levels of Ang I and Ang II, mainly in lumbar adipose tissue, and limited the gain in fat mass in young mice. Interestingly, the effects of aliskiren were independent of the type of nutrition (regular or high fat) suggesting that aliskiren might also induce changes in adipose tissue of lean subjects (Stucchi et al., 2009). Finally, in view of the role of RAAS in electrolyte and volume homeostasis, the effects of high salt diet on this system were studied in tissue interstitial fluid and biopsies from subcutaneous abdominal adipose tissue from young men (Engeli et al., 2006). The results clearly showed that adipose-tissue RAAS is not part of a feedback mechanism regulating sodium homeostasis and blood pressure (Engeli et al., 2006).

3.2. Insulin

Insulin is an important, well established stimulator of liver AGT, but conflicting reports have been published regarding its effect on fat AGT. Although streptozotocin-induced insulin deficiency in rats was linked to a fall of adipose tissue AGT expression, which was restored by insulin treatment, these effects were difficult to discern from the general impact of experimental diabetes (Cassis 1992). Insulin supplementation was reported not to affect the secretion of AGT from primary adipocytes extracted from Obese Zucker rats (Turban et al., 2001) but increased AGT expression in human abdominal subcutaneous adipocytes at the protein and mRNA levels (Harte et al., 2003; Jones et al., 1997). Still in other reports, actual insulin-dependent suppression of mRNA expression and the secretion of AGT from Ob1771 and 3T3-F442A adipose cell lines was seen (Aubert et al., 1998). It should be noted that the latter study was done with cell-lines and may not be necessarily extrapolated to the *in vivo* setting.

3.3. Ang II

Ang II is one of a series of known activators of hepatic AGT (e.g., estrogens, triiodothyronine, and glucose) which failed to affect fat cell AGT (Aubert et al., 1997; Jones et al., 1997). It is noteworthy however that the lack of Ang II effect could have been fortuitous due to opposing concomitant effects on AT1R and AT2R. Indeed, in mice with AT2 receptor deficiency, adipose AGT expression clearly increased, and this effect was blocked by an AT1R antagonist (Thatcher et al., 2009). Chronic infusion of Ang II robustly stimulated AGT and $AT_{1a}R$ mRNA in adipose tissue (Lu et al., 2007), but not in the liver. In Ang II-infused mice, plasma AGT concentrations paralleled adipose AGT mRNA expression. These results are consistent with a positive-feedback loop where Ang II regulates adipose AGT via activation of the $AT_{1a}R$.

3.4. Cyclic adenosine monophosphate (cAMP)

The role of cAMP in regulating ATG expression and secretion is of interest since (1) levels of this molecule are increased in adipocytes upon β–adrenergic stimulation; (2) cAMP is a positive regulator of adipogenesis; and (3) there is a clear link between fat body mass and elevated sympathetic stimulation. A study with cultured primary rat differentiated preadipocytes showed that agents known to increase intracellular cAMP (FSK, IBMX) and the membrane-permeable cAMP analog 8–BrcAMP induce an increase in the ATG mRNA level in differentiated rat preadipocytes via the protein kinase A–dependent pathway. In rat adipose tissue fragments, the same positive effect was observed not only on ATG mRNA but also on ATG protein secretion (Serazin et al., 2004).

3.5. Glucocorticosteroids

Based on experiments with dexamethasone–treated 3T3-L1 cells, it was suggested that glucocorticoids play an important role in the expression of fat cell AGT gene (Saye et al., 1989). Further experiments with rodent cell lines Ob1771 and 3T3-F442A as well as explants of rat periepididymal adipose tissue showed that glucocorticoids regulate AGT gene transcription in late differentiated adipocytes, interacting with the glucocorticoid receptor (GR) (Aubert et al., 1997). Mice that were genetically modified to overexpress adipose tissue 11β hydroxysteroid dehydrogenase type 1(11β HSD-1), the enzyme which converts inactive cortisone to active cortisol, developed abdominal obesity and had about threefold increased expression of AGT gene in their adipose cells. The increase in adipose levels of cortisol did not correlate with its plasma levels which remained unchanged (Masuzaki et al., 2001). These features of the transgenic mice are similar to those observed in humans with metabolic syndrome (Rask et al., 2002). Based on these results it has been suggested that increased fat tissue cortisol content leads to excessive GR activation with the ensuing stimulation of GR inducible genes, including AGT (Jain et al., 2005).

3.6. TNF-α

In cultured cryo-preserved human subcutaneous preadipocytes, derived from human adipose tissue of female subjects, treatment with human recombinant TNF-α (5 or 100 ng/ml) resulted in a significant reduction in AGT mRNA levels (Wang et al., 2005). However TNF-α increased renin protein secretion in cultured 3T3 cells (Fowler et al., 2009a).

3.7. Androgens and estrogens

Both adipocyte metabolism and blood pressure development are, to some extent, gender-related and potential sex-dependent differential activation of Ang II is therefore of much interest (Chen et al., 1992). That adipocyte AGT expression and secretion driven by androgens is suggested by the finding that ATG expression decreased after castration but was fully restored in response to testosterone treatment. Moreover, an androgen receptor antagonist prevented the positive *in vitro* influence of androgens on ATG mRNA expression in adipocytes (Serazin-Leroy et al., 2000). In contrast, estradiol had no effect on AGT mRNA in the preadipocyte clonal cell line Ob1771 (Aubert et al., 1997).

3.8. Free Fatty Acids (FFAs)

Elevated FFA were shown to enhance Ang II production in mononuclear and polymorphonuclear cells and to cause Ang II-dependent leukocyte activation, a process that results in endothelial dysfunction partially via oxidative stress (Azekoshi et al., 2010). Interference of the FFA-rich environment in fat tissue with local vasodilator mechanisms could augment the vasoconstrictor response to Ang II, thus reducing blood supply to fat cells. There is also evidence that in committed preadipocytes the AGT gene can be upregulated by long chain fatty acids and downregulated in response to fatty acid removal (Safonova et al., 1997), this provides a potential link between the fatty acid rich milieu in adipose tissue and the ability of adipocytes to produce AGT. In contrast, fatty acids were not found to affect renin gene expression or protein secretion in 3T3-L1 adipocytes (Fowler et al., 2009a).

3.9. Fat RAAS in aging

RAAS is regarded a positive regulator of hypertrophic enlargement of adipose tissue, in good accordance with the fact that and

body fat increases with age. However, in a presumable contraintuitive manner plasma levels of systemic RAAS components seem to decrease with age (Abadir 2011). In one study with rats, by the age of 24 weeks, AGT expression became significantly greater in epididymal (a rodent equivalent of visceral) fat than in subcutaneous adipose tissue (Adams et al., 2002). In a study that compared 9–26 week-old rats in terms of AGT, ACE and AT1R mRNA expression in epididymal adipose tissue, AGT and ACE expression decreased with increased age and adiposity (Krskova et al., 2011). These RAAS parameters correlated with the expression of the adiposity-dependent proteins leptin, adiponectin, the insulin-dependent glucose transporter (GLUT4) and PPARγ. AT1R mRNA and protein expression, however, was significantly elevated in 26-week-old rats but this was not reflected in changes in Ang II binding. It is noteworthy that inhibition of Ang II activity by targeted disruption of the Agtr1a gene (encoding $AT_{1A}R$) in mice translates into marked prolongation of life span. The absence of $AT_{1A}R$ protected multiple organs from oxidative damage and the alleviation of aging-like phenotype associated with increased number of mitochondria and upregulation of the pro-survival gene sirtuin 3 (Cassis et al., 2010). Interaction between age and the evolution of obesity with respect to fat Ang II is also suggested by the observation that Ang II -induced facilitation of sympathetic neurotransmission in brown fat is decreased in adult obese rats relative to young lean rats (Cassis 1994).

4. Effect of fat tissue RAAS on systemic/circulating RAAS

4.1. Fat AGT contributes to circulating and non-fat tissue AGT

There is evidence that adipocyte-endogenous AGT contributes to the systemic RAAS and to blood pressure control (Yiannikouris et al., 2012). Selective adipocyte AGT deficiency lowered plasma concentrations of AGT by 24–28%, compared with controls; this was in association with reduced systolic blood pressure. Mice whose AGT expression is restricted to adipose tissue have increased AGT circulating in the blood stream whereas mice that overexpress adipose AGT do not only have increased circulating AGT levels but are also hypertensive, attesting to the functional importance of the spillover of fat AGT to the systemic circulation (Massiera et al., 2001a). In one report with hypertensive mice, the adipocyte-specific AGT overexpression was linked to a parallel increase in kidney AGT expression (Kim et al., 2006), thus suggesting that fat cell RAAS contributes to RAAS beyond the local adipocyte environment.

4.2. Fat-tissue derived Ang II may be released to the circulation under increased sympathetic drive

In obese, but not in lean, human subjects AGT was shown to be released from adipose tissue and skeletal muscle during β–adrenergic stimulation, which likely contributes a concomitant increase in plasma Ang II concentrations under these conditions. Thus, increased sympathetic system activity in obese subjects can contribute to the release of RAAS components from the excessive fat tissue to the circulation, thereby supporting a systemic rise in blood pressure (Goossens et al., 2006, 2007b).

5. RAAS, Ang II and fat tissue metabolism

5.1. Rate of TG storage and blood flow

The uptake of meal fatty acids depends on the expression of adipocyte lipoprotein lipase (LPL). LPL mRNA expression is higher in abdominal than in gluteal adipose cells. LPL activity is also higher in abdominal adipocytes from men and in gluteal adipocytes from women when compared with the other depots respectively (Arner et al., 1991; Pouliot et al., 1991). Ang II causes vasoconstriction and catecholamine secretion, which can jointly decrease blood flow (Matsubara 1998; Moan et al., 1996). Chronic exposure to the non-specific β-adrenergic agonist isoproterenol leads to tissue specific alterations in LPL activity (Deshaies et al., 1993; Saranteas et al., 2003). Ang II was shown to suppress adipocyte LPL expression (Saiki et al., 2008), whereas AR1R antagonism can increase fat cell LPL (Saiki et al., 2006).

5.2. Lipolysis

Lipolysis involves the hydrolysis of triglycerides (TG) into FFAs followed by degradation to acetyl units via beta oxidation. Adipocytes from upper-body obese women are less responsive to the insulin induced inhibition of lipolysis compared with lower-body obese women (Dowling et al., 1995; Hosain et al., 2010). Moreover, higher expression of β-adrenoceptors in the abdominal adipocytes results in a four- to fivefold increase in lipolysis of abdominal compared to gluteal adipocytes in response to noradrenaline stimulation (Arner et al., 1990; Wahrenberg et al., 1989). Most published reports are consistent with a predominantly antilipolytic effect of Ang II, with the exception of one report that Ang II has an AT1R-dependent lipolytic effect (Ahima and Flier 2000). The rate of lipolysis is determined predominantly by insulin and β-adrenoceptors, both of which are negatively regulated by RAAS over-activation in an Ang II-dependent manner (Boschmann et al., 2001; Kalupahana et al., 2012). Accordingly, lipolysis was dose-dependently and strongly inhibited by physiological Ang II concentrations in human subcutaneous adipocytes of normal-weight and obese subjects, suggesting a tonic suppression of lipolysis in vivo (Goossens et al., 2007a). Femoral fat depots seem to be more sensitive to the inhibitory effect of Ang II on lipolysis (Boschmann et al., 2001).

Ang II dose-dependently reduced the perfusion to-, and inhibited basal, but not isoproterenol-stimulated lipolysis in- gluteo-femoral adipose tissue (Boschmann et al., 2001). Excess secretion of Ang II in obesity can reduce adipose-tissue blood flow, directly and possibly via stimulation of α2-adrenoceptors (English and Cassis 1999). This may impact fat by promoting FFA accumulation, which along with inhibition of lipolysis shifts the balance towards re-esterification (Lonnroth and Smith 1992) and also by reducing oxygen delivery, favoring fat tissue hypoxia. Ang II can also enhance lipogenesis by directly increasing the activity and expression of key lipogenic enzymes, leading to increased TG synthesis and storage, ultimately resulting in "fatter" and hence larger fat cells. Finally, Ang II can interfere with lipid metabolism as evidenced by its ability to reduce high density lipoprotein (HDL) and increase cholesterol storage in association with the translocation of scavenger receptor type B1 (SR-B1) proteins to the plasma membrane in adipose tissue. This was also documented in transgenic mice overexpressing AGT in their adipose tissue (Tondu et al., 2005; Yvan-Charvet et al., 2007).

6. Adipose RAAS, Ang II and preadipocyte differentiation

Adipose mass can increase via adipocyte hypertrophy and through enhanced adipocyte proliferation and differentiation. Ang II was reported to either inhibit or accelerate preadipocyte differentiation in vitro, apparently reflecting variation in the experimental setting. Most published data, however, support the notion that Ang II inhibits preadipocyte differentiation (Brucher et al., 2007; Darimont et al., 1994; Fuentes et al., 2010; Janke et al., 2002; Sarzani et al., 2008a; Tomono et al., 2008). The observation that visceral fat preadipocytes are more sensitive to the

AT1R-dependent inhibition of differentiation and that this effect is directly related to BMI in obese subjects is particularly significant for the development of dysfunctional visceral fat (Brucher et al., 2007). Concordant with this notion is the finding that AT1R antagonism appears to accelerate adipocyte differentiation (reviewed in Iwai and Horiuchi 2009). Adipocyte differentiation is inversely correlated with insulin sensitivity, and RAAS blockade may delay the onset of T2D by promoting the differentiation of adipocytes into mature adipocytes (Sharma et al., 2002). This allows proper eutopic storage sites for fat derived from overnutrition and minimizes the deposition of toxic ectopic fat in non-adipose tissues such as skeletal muscle, liver, heart and even the pancreatic islets. The latter effect might also protect β-cells from being functionally and structurally disabled by adjacent ectopic fat cells.

Not only can circulating or exogenous RAAS components (e.g., Ang II in cultured preadipocyte) affect adipose tissue differentiation but the expression level of endogenous fat RAAS per se appears to depend on the differentiation process and/or phase, thus indirectly suggesting that it very likely plays a role in the progression of differentiation. In one report, renin mRNA expression and protein enzymatic activity were un-detectable in preadipocytes, but became rather evident upon differentiation (Fowler et al., 2009a). TNF-α, a naturally occurring product in adipose tissue, which is apparently upregulated in dysfunctional adipocytes (reviewed in Stern et al., 2007), markedly increased renin protein secretion in cultured 3T3 cells (Fowler et al., 2009a). In human preadipocytes, the differentiation process involves auto-generation of Ang II through both the renin system and non RAAS pathways, and the latter may be a more important contributor. In parallel, AT1R and AT2R gene expression increases transiently during early differentiation and then rapidly declines (Ye et al., 2009). Further, AT2R deficiency reportedly retards fat cell differentiation (Iwai et al., 2009).

It has been reported that overexpression of AGT in mice leads to a slight but significant decrease in adipose cell number, thus revealing an inhibitory effect of Ang II on preadipocyte differentiation in vivo (Yvan-Charvet et al., 2009). On the other hand, despite the reduced adipose cell number, local production of AGT in adipose tissue clearly promotes fat mass enlargement. Moreover, Ang II was found to increase differentiation of human preadipocytes isolated from both visceral and perirenal adipose tissue (Sarzani et al., 2008a). The latter view is supported by the study of Crandall et al. who showed that Ang II is able to induce cell cycle G1 phase progression of human preadipocytes through AT1Rs by increasing cyclin D1-dependent kinase (Crandall et al., 1999). Probably Ang II, acting through the AT1 receptors, has a proliferative effect on preadipocytes coupled with a differentiating activity that results in an increased number of smaller, healthier, adipocytes (Sarzani et al., 2008b). Since this is discordant with other reports (Brucher et al., 2007; Darimont et al., 1994; Janke et al., 2002; Sarzani et al., 2008a; Tomono et al., 2008), such effects could be depot-specific or relate to time/site dependent differential expression of AT1R/AT2R expression.

7. RAAS, Ang II and adipocyte volume and hypertrophy: Ang II and fat mass

RAAS integrity is important for the development of fat tissue and also for the ability of adipose tissue to properly expand in response to caloric excess. Experimental maneuvers which either block or accentuate RAAS are generally in line with this concept. Negative regulation of Ang II production appears to diminish fat tissue accumulation. For example, mice lacking AGT were protected from high-fat-diet induced obesity and featured adipose tissue hypotrophy (Massiera et al., 2001b). Fat mass expansion was also not seen in mice lacking the renin gene and fed on high fat diet (Takahashi

et al., 2007). Similarly, the absence of ACE expression in mice prevented diet-induced obesity (Jayasooriya et al., 2008). At least a permissive role for adipose tissue expansion in response to dietary challenge was also shown for both AT1R and AT2R as mice lacking either of these receptors were resistant to obesity-induced by high fat intake (Kouyama et al., 2005; Yvan-Charvet et al., 2005). Obviously, while these findings underscore the role of RAAS in fat expansion, systemic negative manipulations of RAAS components neither exclusively nor directly implicates local fat tissue RAAS in this process. More specific fat RAAS targeting was achieved in transgenic mice overexpressing adipose tissue AGT, which resulted in higher fat mass than wild-type mice (Massiera et al., 2001a). Apparent excessive/anomalous/imbalanced activation of AT1R through immunization of pregnant rats against the second extracellular loop of the AT1R resulted in increased visceral adipose tissue, increased fatty liver, increased TGs, decreased HDL cholesterol, and decreased adiponectin levels in the first generation offspring. This highlighted the role of normal AT1R function for balanced adipose disuse evolution and distribution (Zhang et al., 2012). These data provide some direct evidence for the role of adipose AGT in adipose tissue growth (Massiera et al., 2001a). Finally, mice lacking the Mas receptor exhibited increased abdominal fat mass associated with higher adipose tissue AGT expression (Santos et al., 2008).

An important extension to the role of RAAS in fat mass expansion is the understanding that it could play a role in the deposition of ectopic fat as well (Sui et al., 2010). Redistribution of fat, renal fat deposition and hyperlipidemia can accompany chronic renal failure (CRF). While uni-nephrectomized rats showed increased renal adipogenesis with AGT and Ang I/II in renal tubular cells and adipocytes, treatment with ACE inhibitor restored normolipidemia and normalized renal adipogenesis and lipid deposition. Thus, not only eutopic, but also ectopic fat deposition apparently requires intact local RAAS function.

8. Central involvement of RAAS in adipose tissue homeostasis

Complex interactions link central RAAS with adipose tissue RAAS. Chronic intracerebroventricular (icv) Ang II infusion reduced body and adipose tissue mass (de Kloet et al., 2011). This could mimic a putative effect of centrally generated Ang II response to central or peripheral cues. Additionally, this effect could serve a negative feedback through which Ang II spillover from excessive adipose tissue to the circulation becomes sufficiently high to access the brain, thus potentially counteracting the peripheral fat building effect of adipose-derived Ang II. Centrally mediated Ang II-dependent reduction in energy storage is consequent to both a decrease in food intake and an increase in energy expenditure. Moreover, with centrally administered Ang II, indices of sympathetic activation are elevated in both brown and white adipose tissues (BAT and WAT). This implies that Ang II acts centrally to enhance BAT thermogenesis and WAT lipolysis, presumably contributing to the state of negative energy balance. Moreover, central Ang II administration increased hypothalamic expression of corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH), both of which can elicit anorixogenic effects (de Kloet et al., 2011). On the other hand, AGT- and AT2-deficient mice show increased energy expenditure, apparently resulting from increased locomotor activity and whole-body lipid oxidation (Massiera et al., 2001b; Yvan-Charvet et al., 2005). These findings could be related in part to the regulatory effect of Ang II on adiponectin secretion, which controls muscle fatty acid oxidative capacity (Clasen et al., 2005; Furuhashi et al., 2003). Taken together, these studies suggest that reduced Ang II signaling might provide some protection from fat mass enlargement in mice by increasing peripheral energy expenditure and whole-body lipid oxidation.

9. Adipocyte dysfunction and systemic RAAS

Adipocytes are not a merely energy reservoirs but rather a major endocrine tissue that synthesizes and secretes adipokines such as proinflammatory cytokines, acute-phase response proteins, chemotactic/chemoattractants, eicosanoids, prostaglandins; as well as potential anti-inflammatory effectors such as adiponectin and IL-10 (Bays et al., 2007). "Dysfunctional adipocytes" or "angry fat" is a relatively loose term used to describe fat cells which, due caloric excess, accumulate excessive fat and undergo marked increase in size. Dysfunctional/mutated proteins/enzymes or incitement by surrounding factors such as M1 macrophages, not only produce increased amounts of adipokines, but sustain unregulated excessive lipolysis leading to an increase in circulating FFAs. Insulin resistance and/or insufficiency jointly with increased sympathetic activity, which is associated with obesity, further accelerate lipolysis. The ensuing rise in circulating FFA levels leads to the ectopic deposition of fat which in organs such as the liver, skeletal muscle, and heart further aggravates insulin resistance and induces mitochondrial dysfunction and tissue injury. Such injury to pancreatic β-cells can result in reduction in the ability to secrete insulin and eventually induce β-cell apoptosis. This vicious cycle accentuates insulin resistance and can lead to T2D. Improvement of adipocyte function and/or replacement of poorly functioning adipocytes by younger, fully functional, recently differentiated and yet unimpaired fat cells could retard unwanted metabolic sequels of the "angry fat" or "adiposities". Preadipocytes are fibroblast-like cells comprising a sizable fraction of the cell population in fat tissue (e.g., 15–50% according to one report), which, in response to appropriate cues, differentiate into adipocytes. Differentiation is initiated through signaling pathways activated by fatty acids, IGF-1, glucocorticoids, and other stimuli and is followed by a cascade of transcription factors that underlies acquisition and maintenance of the fat cell phenotype (Rosen 2005). Normal fat cell turnover, involves differentiation of preadipocytes into adipocytes and apoptosis of large, old adipocytes (Boney et al., 2001).

Circulatory RAAS component levels are clearly affected by adipose tissue mass. Visceral obesity is associated with inappropriate or even elevated levels of plasma renin activity and/or aldosterone despite increased sodium intake, sodium/water retention, central blood volume, and blood pressure (Goodfriend et al., 1999). Additionally, compared to lean women, obese women have higher circulating AGT, renin, aldosterone, ACE and lower AGT gene expression in adipose tissue but higher fat-derived secreted AGT (Yasue et al., 2010). Such non-suppressed activity of RAAS could play a key role in hypertension and subsequent cardiovascular complications in obese subjects. Weight reduction (approximately 5%), on the other hand, reduced AGT, renin and aldosterone levels and decreased ACE expression (Engeli et al., 2005).

10. Ang II and adipose tissue inflammation

Obesity is often associated with low-grade inflammation, predominantly of the adipose tissue itself. As fat mass expands to other sites, this inflammation is also seen at ectopic fat depots, e.g., the perivascular tissue, muscle, liver and the pancreas as well as fat-free sites, such as the hypothalamus. Inflammation may, in fact, have a significant role in the onset of obesity (Hotamisligil 2006). Ang II can promote inflammation through the stimulation of chemokine secretion and the induction of increased oxidative stress (Daugherty et al., 2000; Harrison et al., 2003). For example, in preadipocytes extracted from rat adipose tissue Ang II increased mRNA and protein of monocyte chemoattractant protein-1 (MCP-1). Similarly, Ang II infusion to rats increased mRNA expression of MCP-1 in adipose tissue (Tsuchiya et al., 2006). Conversely,

blockade of AT1 receptors in mice fed with diet-induced obesity and genetically obese mice reduced the reactive oxygen species (ROS) originating from adipose tissue (Kurata et al., 2006).

Ang II can also recruit macrophages to fat tissue, thus further enhancing local inflammation. Indeed, infusion of Ang II to obese mice increased macrophage infiltration into periaortic and visceral adipose tissue. Infiltration of periaortic fat was further associated with increased tendency to develop abdominal aortic aneurysms (Police et al., 2009). Diet induced obesity per se reportedly not only increases the population of macrophages in the adipose tissue, but leads to "macrophage polarization", i.e., a phenotypic switch in adipose tissue macrophages from an anti-inflammatory M2 state to a proinflammatory M1 state (see Fig. 1). A role for endogenous fat tissue Ang II in this process is suggested by the observation that the AT1R blocker telmisartan reduced the mRNA expression of CD11c and TNF-α, M1 macrophage markers, and significantly increased the expressions of M2 markers, such as CD163, CD209, and macrophage galactose N-acetyl-galactosamine specific lectin (Mgl2) in adipose tissue of high-fat fed mice (Fujisaka et al., 2011). This concept has been further refined by a very recent report indicating that whereas $AT_{1a}R$ knockout mice subjected to high fat diet can still develop a proinflammatory visceral and renal macrophage population, further treatment with an AT1R blocker, which affects both $AT_{1a}R$ and $AT_{1b}R$, abolished renal macrophage infiltration with inhibition of renal M1 and upregulation of M2 macrophage markers in obese wild type mice. Thus, endogenous Ang II may modulate fat tissue macrophage polarization through subtle differential interaction with the $AT_{1a}R$ and $AT_{1b}R$ subtypes (Ma et al., 2011). Mast cells can also infiltrate fat tissue and are more densely found in fat depots of obese subjects (Tanaka et al., 2011). Since mast cells contain both renin and chymase, a family of serine proteases that convert Ang I to Ang II (Zheng et al., 2012), their presence in adipocytes can provide an additional source for angiotensin peptides, including Ang II. Collectively, fat infiltration by inflammation-related cells may contribute to the increased systemic inflammation which apparently contributes to the development of insulin resistance and eventually T2D.

Ang II was shown to inhibit the secretion of adiponectin, an adipocyte specific peptide hormone that exerts anti-inflammatory and insulin sensitizing effects (Kadowaki et al., 2006). Concordantly, adiponectin secretion is enhanced by RAAS inhibition in human subjects (Furuhashi et al., 2003). In obese mice the ARB olmesartan ameliorated dysregulation of adipocytokines and lowered TNF-α, plasminogen activator inhibitor-1 (PAI-1), MCP1, and serum amyloid A3 (Kurata et al., 2006).

A critical facet of adipose tissue inflammation is the increased oxidative stress, typical of dysfunctional fat. In addition to the oxidative effect exerted by inflammatory cells and cytokines, fatty acids per se that are continuously released in the adipose milieu due to lipolysis, especially under insulin resistance/insufficiency, are potent instigators of oxidative stress, acting through activation of NADPH oxidase (Furukawa et al., 2004). Pro-lipolytic mechanisms, then, indirectly enhance adipose tissue oxidative stress. Ang II increases oxidative stress via AT_1R activation which leads to increased generation of ROS, partly through activation of NADPH oxidase. Released ROS can oxidize lipids, protein, and DNA which collectively leads to cellular injury. ROS can also induce and/or perpetuate inflammation via activation of transcription factors such as TNF-α, MCP-1, IL-6 (reviewed in Cooper et al., 2007), thereby fostering insulin resistance, which at the fat cell level, is conducive of further lipolysis and release FFAs. In inhibiting pre-adipocyte differentiation, Ang II also indirectly induces shifting of fat formed due to caloric excess from storage in newly formed small adipocytes to large adipocytes, whose further enlargement elicits increases cell oxidative stress and mitochondrial dysfunction (Stern et al., 2007). It is only expected, then, that in mice with
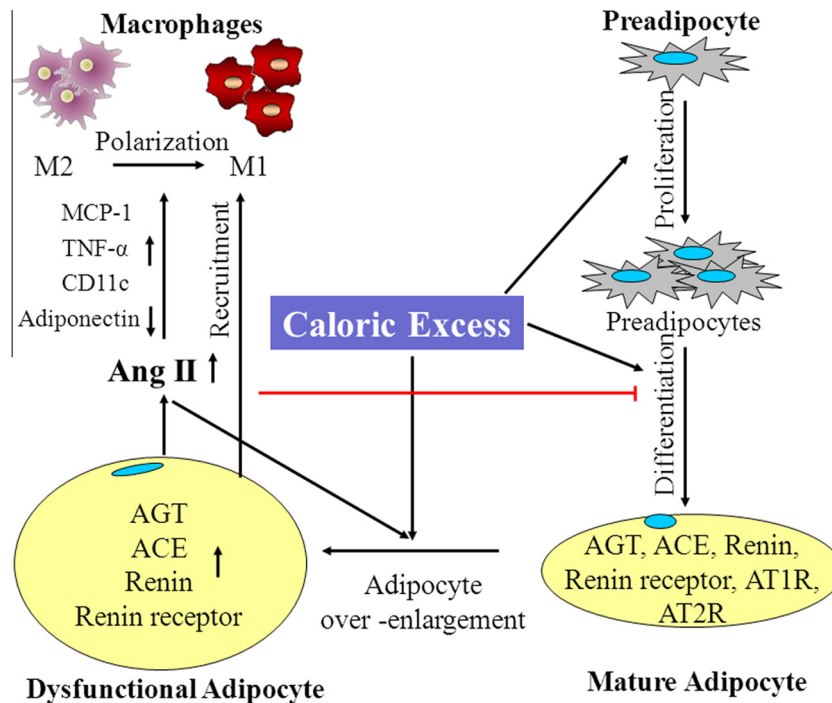
Fig. 1. The role of Ang II in macrophage polarization and adipocyte dysfunction. Ang II, a major product of the RAAS, retards preadipocyte differentiation, thereby affording the channeling of caloric excess to storage in existing adipocytes. Large adipocytes form and tend to become dysfunctional, exhibit increased lipolytic activity, secrete pro-inflammatory adipokines and attract inflammatory cells. Ang II also plays a role in "macrophage polarization" by inducing an increase in the mRNA expression of CD11c and TNF-α, M1 macrophage markers in adipose tissue, and inhibits the secretion of adiponectin, an anti-inflammatory adipocyte specific peptide hormone.

diet-induced or genetic obesity AT1R blockade reduces adipose tissue ROS formation (Kurata et al., 2006). In several systems, Ang II induced insulin resistance, which is attributed, in part, to increased oxidative stress, possibly through impaired insulin signaling located downstream to PI3-kinase activation, inhibition of GLUT-4 or alternative pathways (Ogihara et al., 2002; Townsend 2003). AT2R may also affect glucose homeostasis in adipocytes: whereas AT1R blocker increases insulin-induced glucose uptake in both white and brown adipose tissue, uptake is impaired in white adipocytes of transgenic AT2R-null mice, thus suggesting that AT1R and AT2R activation is mutually antagonistic in terms of glucose uptake in fat tissue (Shiuchi et al., 2004). Recent large-scale clinical trials showed that RAAS blockade with either ACE inhibitors or ARBs consistently prevented new-onset T2D, probably reflecting improved insulin sensitivity (Jandeleit-Dahm et al., 2005). These data are consistent with this experimental background in fat cells, particularly since ARBs favorably modulate fat cell size and inflammatory gene expression (Munoz et al., 2009).

11. Fat RAAS, fibrosis and hypoxia/hyperoxia

11.1. Fibrosis

Adipocytes are embedded in an extracellular matrix which functions as a skeleton of mechanical support, but has in addition, important emerging role in fat tissue expansion, function, susceptibility to inflammation and response to attempted weight loss. Collagen 6 appears to be a dominant player in the fibrous element of fat (Khan et al., 2009). Extracellular matrix remodeling is likely an important process during weight gain, as collagen 6 α3-subunit (COL6A3) is increased in visceral fat of obese subjects and increased during overfeeding, suggesting that it is important in adipose tissue expansion (Khan et al., 2009; Pasarica et al., 2009a). Further, recent evidence indicates that subcutaneous fat from ob-

ese children displays significant increase of interstitial fibrosis (Sbarbati et al., 2006). This was further confirmed in adult obese subjects, in whom the fibrotic matrix was localized to the peri-adipcyte milieu (Henegar et al., 2008). Rather significantly, 3 months following bariatric surgery fat tissue fibrosis did not regress along with fat mass shrinkage. Furthermore, overfeeding results in concomitant increase in microvascular density and intercellular matrix and perivascular connective sheaths in human subcutaneous fat, noted even prior to changes in adipocyte size (Tam et al., 2011). In rodents, the absence of collagen 6 results in the uninhibited expansion of individual adipocytes and was paradoxically associated with substantial improvements in whole-body energy homeostasis (Khan et al., 2009). Hence, it is possible that subtle phenotypic alterations of human pre-adipocytes, adipocytes and other cell types residing in fat tissue of obese subjects lead to excessive synthesis of ECM components, such as collagen 6, which can later persist. It is likely that RAAS plays a role in this process, given the pro-fibrotic effects of Ang II as well as aldosterone in other tissues and the stimulation of fat RAAS with overfeeding. Adipose tissue fibrosis may also result from hypoxia (see below).

11.2. Hypoxia and fibrosis

Adipose tissue oxygen content/tension is regulated by adipose tissue blood flow and the rate of fat cell oxygen consumption. Adipose tissue hypoxia may evolve secondary to insufficient rise in blood supply when fat cell mass increases rapidly or during excessive local arterial vasoconstriction which limits oxygen supply to fat cells, such as potentially inducible by excess locally produced Ang II in fat tissue. In rodents, adipose tissue hypoxia was reported in both genetic (ob/ob) and diet-induced obese mouse models (Rausch et al., 2008; Ye et al., 2007). However, studies with human adipose tissue showed either decreased or increased oxygen tension (Goossens et al., 2011; Hosogai et al., 2007; Pasarica et al., 2009b). Reduced oxygen utilization for fat oxidation in adipocytes

of some obese subjects apparently underlies the finding of hyperoxia, rather than hypoxia, despite lesser capillarization of the adipose tissue in obese subjects (Goossens et al., 2011). When hypoxia does evolve in fat tissue of obese animals, however, it induces the expression of hypoxia-inducible factor 1α (HIF1α), which in turn, elicits fibrosis, inflammation and insulin resistance, rather than the expected vascularization (He et al., 2011). Although not specifically shown in adipose tissue, Ang II can increase HIF1α in renal tissue (Zhu et al., 2011), thereby providing yet another mechanism by which RAAS activation may be linked to fat tissue fibrosis and insulin resistance and dysfunction. As suggested by Hayden et al. (2011), fat tissue fibrosis could result in loss of the normal cell–cell and cell-matrix communication, which may in turn disrupt normal paracrine control of adipogenic and metabolic functions and even impede attempted weight loss in the obese.

12. Disruption of RAAS protects from obesity

Overall, experimental and clinical data support the concept that disruption of the RAAS can protect from obesity and/or its sequels. Mice lacking renin showed reduced production of renin-driven peptides of the RAAS such as Ang II and were also protected from obesity (Takahashi et al., 2007). Likewise, mice lacking AGT, AT2R or AT1R were protected from high-fat-diet induced obesity and featured adipose tissue hypotrophy (Massiera et al., 2001b; Yvan-Charvet et al., 2005; Kouyama et al., 2005). Collectively these results suggest a synergistic contribution of AT1 and AT2 in mediating the *in vivo* effect of Ang II on adipose tissue development. The notion of systemic trophic/permissive effect of Ang II on adipose tissue development was further supported by the finding that ACE KO-mice had less body fat, particularly abdominal fat, than wild type controls. The mechanisms implicated in protection from obesity in this model also involved increased energy expenditure and enhanced lipolysis in adipose depots (Jayasooriya et al., 2008). Finally, RAAS blockade via ACEI, ARBS or a renin inhibitor prevented fat mass enlargement (de Kloet et al., 2009; Lee et al., 2008; Mathai et al., 2008; Stucchi et al., 2009). In humans, RAAS inhibition through ACEI or ARBs is known to reduce the incidence of T2D (Tocci et al., 2011). Complementary to these data is the evidence that one of the countering arms of Ang II driven effects, that of the Ang1–7/Mas receptor system, acts in the opposite direction: mice lacking the Mas receptor exhibited increased abdominal fat mass associated with higher adipose tissue AGT expression, thereby suggesting a tight regulation of Ang II production by Ang (1–7) in adipose tissue (Santos et al., 2008).

13. Fat RAAS and insulin resistance: an integrated overview

Fat tissue RAAS induces and aggravates insulin resistance through both local and systemic mechanisms. As schematically shown in Fig. 1, local the expression of the key components of RAAS in adipose tissue increases along with fat cell differentiation (Fowler et al., 2009a). In fact, fat mass enlargement in response to caloric excess requires the presence of the full cascade of fat RAAS. Yet, Ang II, a major product of this system, retards differentiation, thereby affording the channeling of caloric excess to storage in existing adipocytes. Large, "fatter" adipocytes thus form and tend to become dysfunctional to exhibit increased lipolytic activity, secrete pro-inflammatory adipokines and to attract inflammatory cells such as M1 macrophages to adipose tissue. A state of "adiposities" evolves, leading to the increased release FFA, adipokines such as resistin, cytokines such as IL6 and TNF-α, and chemoattractants such as MCP-1. Local insulin resistance is jointly enhanced by compounds, which translates into further enhancement of lipolysis. The latter increases oxidative stress, such that adipocyte dysfunc-
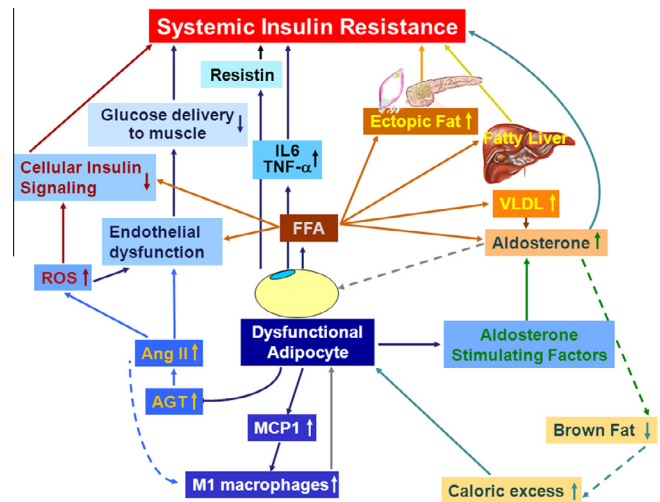

Fig. 2. Dysfunctional adipocytes and systemic insulin resistance. Ang II inhibits insulin-dependent glucose uptake by multiple mechanisms including: the induction of endothelial dysfunction, which diminishes insulin-dependent glucose transport to target cells, such as skeletal muscle; disruption of insulin cell signaling by increasing ROS formation; and direct interference with multiple insulin signaling elements in skeletal muscle. Adipocytes also increase the secretion of aldosterone, which independently aggravates insulin resistance.

tion and insulin resistance are further augmented. As caloric excess persists, active RAAS is required for fat mass enlargement and ectopic fat deposition, both of which increase the resistance to insulin's actions. Locally produced Ang II can reduce blood supply to adipose depots thereby enhancing local inflammation. Such reduction in local perfusion will also reduce the clearance of released FFA which not only stimulate ROS formation via induction of NADPH oxidase activity, but are shifted back to esterification, a process that increases local fat deposition and adipocyte cell size.

Spillage of fat tissue-derived angiotensinogen and Ang II in obesity contributes to systemic effects of RAAS, as schematically shown in Fig. 2. Ang II inhibits insulin-dependent glucose uptake by multiple mechanisms including the induction of endothelial dysfunction, which diminishes insulin-dependent glucose transport to target cells (e.g., skeletal muscle cells) and disruption of insulin cell signaling by increasing ROS formation and direct interference with multiple insulin signaling elements in skeletal muscle, such as inhibition of insulin-mediated GLUT4 translocation through transient activation of ERK1/2 which inhibit IRS-1/2 and a direct inhibitory nitration of Akt (Csibi et al., 2010). Ang II also increases the secretion of aldosterone and this effect is synergistic with adipose tissue-derived aldosterone stimulating factor (Krug et al., 2007). Aldosterone is yet another enhancer of insulin resistance, whose secretion is stimulated by fat derived compounds including Ang II itself and adipocyte-derived aldosterone stimulating factor(s). Aldosterone increases oxidative stress (Lastra et al., 2008), which leads to insulin receptor substrate 1 degradation, reduced downstream phosphorylation of Akt which translates into diminished translocation of GLUT-4 translocation to the plasma membrane, resulting in reduced glucose uptake. Recent evidence also indicates that aldosterone increases oxidative stress in cultured fat cells, acting through both MR and GR, thereby assisting in the shift of adipose tissue into a dysfunctional state, which aggravates local and systemic insulin resistance (Limor et al., 2012).

References

Abadir, P.M., 2011. The frail renin–angiotensin system. Clin. Geriatr. Med. 27, 53–66.

Achard, V., Boullu-Ciocca, S., Desbriere, R., Nguyen, G., Grino, M., 2007. Renin receptor expression in human adipose tissue. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292, R274–282.

Achard, V., Tassistro, V., Boullu-Ciocca, S., Grino, M., 2011. Expression and nutritional regulation of the (pro)renin receptor in rat visceral adipose tissue. J. Endocrinol. Invest. 34, 840–846.

Adams, F., Wiedmer, P., Gorzelniak, K., Engeli, S., Klaus, S., Boschmann, M., 2002. Age-related changes of renin–angiotensin system genes in white adipose tissue of rats. Horm. Metab. Res. 34, 716–720.

Aguilar, F., Lo, M., Claustrat, B., Saez, J.M., Sassard, J., Li, J.Y., 2004. Hypersensitivity of the adrenal cortex to trophic and secretory effects of angiotensin II in Lyon genetically-hypertensive rats. Hypertension 43, 87–93.

Ahima, R.S., Flier, J.S., 2000. Adipose tissue as an endocrine organ. Trends Endocrinol. Metab. 11, 327–332.

Alligier, M., Meugnier, E., Debard, C., Lambert-Porcheron, S., Chanseaume, E., Sothier, M., Loizon, E., Hssain, A.A., Brozek, J., Scoazec, J.Y., et al., 2012. Subcutaneous adipose tissue remodeling during the initial phase of weight gain induced by overfeeding in humans. J. Clin. Endocrinol. Metab. 97, E183–192.

Araki, K., Masaki, T., Katsuragi, I., Tanaka, K., Kakuma, T., Yoshimatsu, H., 2006. Telmisartan prevents obesity and increases the expression of uncoupling protein 1 in diet-induced obese mice. Hypertension 48, 51–57.

Arner, P., Hellstrom, L., Wahrenberg, H., Bronnegard, M., 1990. Beta-adrenoceptor expression in human fat cells from different regions. J. Clin. Invest. 86, 1595–1600.

Arner, P., Lithell, H., Wahrenberg, H., Bronnegard, M., 1991. Expression of lipoprotein lipase in different human subcutaneous adipose tissue regions. J. Lipid Res. 32, 423–429.

Aubert, J., Darimont, C., Safonova, I., Ailhaud, G., Negrel, R., 1997. Regulation by glucocorticoids of angiotensinogen gene expression and secretion in adipose cells. Biochem. J. 328, 701–706.

Aubert, J., Safonova, I., Negrel, R., Ailhaud, G., 1998. Insulin down-regulates angiotensinogen gene expression and angiotensinogen secretion in cultured adipose cells. Biochem. Biophys. Res. Commun. 250, 77–82.

Azekoshi, Y., Yasu, T., Watanabe, S., Tagawa, T., Abe, S., Yamakawa, K., Uehara, Y., Momomura, S., Urata, H., Ueda, S., 2010. Free fatty acid causes leukocyte activation and resultant endothelial dysfunction through enhanced angiotensin II production in mononuclear and polymorphonuclear cells. Hypertension 56, 136–U218.

Bays, H., Rodbard, H.W., Schorr, A.B., Gonzalez-Campoy, J.M., 2007. Adiposopathy: treating pathogenic adipose tissue to reduce cardiovascular disease risk. Curr. Treat. Options Cardiovasc. Med. 9, 259–271.

Benson, S.C., Pershadsingh, H.A., Ho, C.I., Chittiboyina, A., Desai, P., Pravenec, M., Qi, N.N., Wang, J.M., Avery, M.A., Kurtz, T.W., 2004. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPAR gamma-modulating activity. Hypertension 43, 993–1002.

Bergman, R.N., Mittelman, S.D., 1998. Central role of the adipocyte in insulin resistance. J. Basic Clin. Physiol. Pharmacol. 9, 205–221.

Boney, C.M., Sekimoto, H., Gruppuso, P.A., Frackelton Jr., A.R., 2001. Src family tyrosine kinases participate in insulin-like growth factor I mitogenic signaling in 3T3-L1 cells. Cell Growth Differ. 12, 379–386.

Boschmann, M., Ringel, J., Klaus, S., Sharma, A.M., 2001. Metabolic and hemodynamic response of adipose tissue to angiotensin II. Obes. Res. 9, 486–491.

Boustany, C.M., Bharadwaj, K., Daugherty, A., Brown, D.R., Randall, D.C., Cassis, L.A., 2004. Activation of the systemic and adipose renin–angiotensin system in rats with diet-induced obesity and hypertension. Am. J. Physiol. Regul. Integr. Comp. Physiol. 287, R943–949.

Brucher, R., Cifuentes, M., Acuna, M.J., Albala, C., Rojas, C.V., 2007. Larger anti-adipogenic effect of angiotensin II on omental preadipose cells of obese humans. Obesity (Silver Spring) 15, 1643–1646.

Caprio, M., Antelmi, A., Chetrite, G., Muscat, A., Mammi, C., Marzolla, V., Fabbri, A., Zennaro, M.C., Feve, B., 2011. Antiadipogenic effects of the mineralocorticoid receptor antagonist drospirenone: potential implications for the treatment of metabolic syndrome. Endocrinology 152, 113–125.

Caprio, M., Feve, B., Claes, A., Viengchareun, S., Lombes, M., Zennaro, M.C., 2007. Pivotal role of the mineralocorticoid receptor in corticosteroid-induced adipogenesis. FASEB J. 21, 2185–2194.

Carey, R.M., Siragy, H.M., 2003. Newly recognized components of the renin–angiotensin system: potential roles in cardiovascular and renal regulation. Endocr. Rev. 24, 261–271.

Carranza, M.C., Torres, A., Calle, C., 1991. Decreased insulin receptor number and affinity in subcutaneous adipose tissue in a patient with primary hyperaldosteronism. Rev. Clin. Esp. 188, 414–417.

Cassis, L.A., 1992. Downregulation of the renin–angiotensin system in streptozotocin-diabetic rats. Am. J. Physiol. 262, E105–109.

Cassis, L.A., 1994. Angiotensin II in brown adipose tissue from young and adult Zucker obese and lean rats. Am. J. Physiol. 266, E453–458.

Cassis, L.A., English, V.L., Bharadwaj, K., Boustany, C.M., 2004. Differential effects of local versus systemic angiotensin II in the regulation of leptin release from adipocytes. Endocrinology 145, 169–174.

Cassis, L.A., Police, S.B., Yiannikouris, F., Thatcher, S.E., 2008. Local adipose tissue renin–angiotensin system. Curr. Hypertens. Rep. 10, 93–98.

Cassis, L.A., Saye, J., Peach, M.J., 1988. Location and regulation of rat angiotensinogen messenger RNA. Hypertension 11, 591–596.

Cassis, P., Conti, S., Remuzzi, G., Benigni, A., 2010. Angiotensin receptors as determinants of life span. Pflugers Arch.-European J. Physiol. 459, 325–332.

Chen, Y., Naftilan, A., Oparil, S., 1992. Androgen-dependent angiotensinogen and renin messenger RNA expression in hypertensive rats. Hypertension 19, 456–463.

Clasen, R., Schupp, M., Foryst-Ludwig, A., Sprang, C., Clemenz, M., Krikov, M., Thone-Reineke, C., Unger, T., Kintscher, U., 2005. PPARgamma-activating angiotensin type-1 receptor blockers induce adiponectin. Hypertension 46, 137–143.

Cooper, S.A., Whaley-Connell, A., Habibi, J., Wei, Y., Lastra, G., Manrique, C., Stas, S., Sowers, J.R., 2007. Renin–angiotensin–aldosterone system and oxidative stress in cardiovascular insulin resistance. Am. J. Physiol. Heart Circ. Physiol. 293, H2009–2023.

Crandall, D.L., Armellino, D.C., Busler, D.E., McHendry-Rinde, B., Kral, J.G., 1999. Angiotensin II receptors in human preadipocytes: role in cell cycle regulation. Endocrinology 140, 154–158.

Crandall, D.L., Herzlinger, H.E., Saunders, B.D., Armellino, D.C., Kral, J.G., 1994. Distribution of angiotensin-II receptors in rat and human adipocytes. J. Lipid Res. 35, 1378–1385.

Csibi, A., Communi, D., Müller N & Bottari, S.P., 2010. Angiotensin II inhibits insulin-stimulated GLUT4 translocation and Akt activation through tyrosine nitration-dependent mechanisms. PLoS ONE 5, e10070.

Dall'Asta, C., Vedani, P., Manunta, P., Pizzocri, P., Marchi, M., Paganelli, M., Folli, F., Pontiroli, A.E., 2009. Effect of weight loss through laparoscopic gastric banding on blood pressure, plasma renin activity and aldosterone levels in morbid obesity. Nutr. Metab. Cardiovasc. Dis. 19, 110–114.

Darimont, C., Vassaux, G., Ailhaud, G., Negrel, R., 1994. Differentiation of preadipose cells - paracrine role of prostacyclin upon stimulation of adipose-cells by angiotensin-II. Endocrinology 135, 2030–2036.

Daugherty, A., Manning, M.W., Cassis, L.A., 2000. Angiotensin II promotes atherosclerotic lesions and aneurysms in apolipoprotein E-deficient mice. J. Clin. Invest. 105, 1605–1612.

de Kloet, A.D., Krause, E.G., Kim, D.H., Sakai, R.R., Seeley, R.J., Woods, S.C., 2009. The effect of angiotensin-converting enzyme inhibition using captopril on energy balance and glucose homeostasis. Endocrinology 150, 4114–4123.

de Kloet, A.D., Krause, E.G., Scott, K.A., Foster, M.T., Herman, J.P., Sakai, R.R., Seeley, R.J., Woods, S.C., 2011. Central angiotensin II has catabolic action at white and brown adipose tissue. Am. J. Physiolo. Endocrinol. Metab. 301, E1081–E1091.

de Kloet, A.D., Krause, E.G., Woods, S.C., 2010. The renin–angiotensin system and the metabolic syndrome. Physiol. Behav. 100, 525–534.

Deshaies, Y., Geloen, A., Paulin, A., Marette, A., Bukowiecki, L.J., 1993. Tissue-specific alterations in lipoprotein lipase activity in the rat after chronic infusion of isoproterenol. Horm. Metab. Res. 25, 13–16.

Dowling, H.J., Fried, S.K., Pi-Sunyer, F.X., 1995. Insulin resistance in adipocytes of obese women: effects of body fat distribution and race. Metab. Clin. Exp. 44, 987–995.

Ehrhart-Bornstein, M., Arakelyan, K., Krug, A.W., Scherbaum, W.A., Bornstein, S.R., 2004. Fat cells may be the obesity-hypertension link: human adipogenic factors stimulate aldosterone secretion from adrenocortical cells. Endocr. Res. 30, 865–870.

Engeli, S., Bohnke, J., Gorzelniak, K., Janke, J., Schling, P., Bader, M., Luft, F.C., Sharma, A.M., 2005. Weight loss and the renin–angiotensin–aldosterone system. Hypertension 45, 356–362.

Engeli, S., Boschmann, M., Frings, P., Beck, L., Janke, J., Titze, J., Luft, F.C., Heer, M., Jordan, J., 2006. Influence of salt intake on renin–angiotensin and natriuretic peptide system genes in human adipose tissue. Hypertension 48, 1103–1108.

English, V., Cassis, L., 1999. Facilitation of sympathetic neurotransmission contributes to angiotensin regulation of body weight. J. Neural Transm. 106, 631–644.

Fallo, F., Veglio, F., Bertello, C., Sonino, N., Della Mea, P., Ermani, M., Rabbia, F., Federspil, G., Mulatero, P., 2006. Prevalence and characteristics of the metabolic syndrome in primary aldosteronism. J. Clin. Endocrinol. Metab. 91, 454–459.

Faloia, E., Gatti, C., Camilloni, M.A., Mariniello, B., Sardu, C., Garrapa, G.G., Mantero, F., Giacchetti, G., 2002. Comparison of circulating and local adipose tissue renin–angiotensin system in normotensive and hypertensive obese subjects. J. Endocrinol. Invest. 25, 309–314.

Ferrario, C.M., Jessup, J., Chappell, M.C., Averill, D.B., Brosnihan, K.B., Tallant, E.A., Diz, D.I., Gallagher, P.E., 2005. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 111, 2605–2610.

Fowler, J.D., Johnson, N.D., Haroldson, T.A., Brintnall, J.A., Herrera, J.E., Katz, S.A., Bernlohr, D.A., 2009a. Regulated renin release from 3T3-L1 adipocytes. Am. J. Physiol. Endocrinol. Metab. 296, E1383–1391.

Fowler, J.D., Krueth, S.B., Bernlohr, D.A., Katz, S.A., 2009b. Renin dynamics in adipose tissue: adipose tissue control of local renin concentrations. Am. J. Physiol. Endocrinol. Metab. 296, E343–350.

Frederich Jr., R.C., Kahn, B.B., Peach, M.J., Flier, J.S., 1992. Tissue-specific nutritional regulation of angiotensinogen in adipose tissue. Hypertension 19, 339–344.

Fuentes, P., Acuna, M.J., Cifuentes, M., Rojas, C.V., 2010. The anti-adipogenic effect of angiotensin II on human preadipose cells involves ERK1,2 activation and PPARG phosphorylation. J. Endocrinol. 206, 75–83.

Fujisaka, S., Usui, I., Kanatani, Y., Ikutani, M., Takasaki, I., Tsuneyama, K., Tabuchi, Y., Bukhari, A., Yamazaki, Y., Suzuki, H., et al., 2011. Telmisartan improves insulin resistance and modulates adipose tissue macrophage polarization in high-fat-fed mice. Endocrinology 152, 1789–1799.

Furuhashi, M., Ura, N., Higashiura, K., Murakami, H., Tanaka, M., Moniwa, N., Yoshida, D., Shimamoto, K., 2003. Blockade of the renin–angiotensin system increases adiponectin concentrations in patients with essential hypertension. Hypertension 42, 76–81.

Furuhashi, M., Ura, N., Takizawa, H., Yoshida, D., Moniwa, N., Murakami, H., Higashiura, K., Shimamoto, K., 2004. Blockade of the renin–angiotensin system decreases adipocyte size with improvement in insulin sensitivity. J. Hypertens. 22, 1977–1982.

Furukawa, S., Fujita, T., Shimabukuro, M., Iwaki, M., Yamada, Y., Nakajima, Y., Nakayama, O., Makishima, M., Matsuda, M., Shimomura, I., 2004. Increased oxidative stress in obesity and its impact on metabolic syndrome. J. Clin. Invest. 114, 1752–1761.

Gembardt, F., Sterner-Kock, A., Imboden, H., Spalteholz, M., Reibitz, F., Schultheiss, H.P., Siems, W.E., Walther, T., 2005. Organ-specific distribution of ACE2 mRNA and correlating peptidase activity in rodents. Peptides 26, 1270–1277.

Giacchetti, G., Faloia, E., Mariniello, B., Sardu, C., Gatti, C., Camilloni, M.A., Guerrieri, M., Mantero, F., 2002. Overexpression of the renin–angiotensin system in human visceral adipose tissue in normal and overweight subjects. Am. J. Hypertens. 15, 381–388.

Giacchetti, G., Ronconi, V., Turchi, F., Agostinelli, L., Mantero, F., Rilli, S., Boscaro, M., 2007. Aldosterone as a key mediator of the cardiometabolic syndrome in primary aldosteronism: an observational study. J. Hypertens. 25, 177–186.

Goodfriend, T.L., Ball, D.L., Egan, B.M., Campbell, W.B., Nithipatikom, K., 2004. Epoxy-keto derivative of linoleic acid stimulates aldosterone secretion. Hypertension 43, 358–363.

Goodfriend, T.L., Kelley, D.E., Goodpaster, B.H., Winters, S.J., 1999. Visceral obesity and insulin resistance are associated with plasma aldosterone levels in women. Obes. Res. 7, 355–362.

Goossens, G.H., Bizzarri, A., Venteclef, N., Essers, Y., Cleutjens, J.P., Konings, E., Jocken, J.W.E., Cajlakovic, M., Ribitsch, V., Clement, K., et al., 2011. Increased adipose tissue oxygen tension in obese compared with lean men is accompanied by insulin resistance, impaired adipose tissue capillarization, and inflammation. Circulation 124, 67–76.

Goossens, G.H., Blaak, E.E., Arner, P., Saris, W.H.M., Van Baak, M.A., 2007a. Angiotensin II: a hormone that affects lipid metabolism in adipose tissue. Int. J. Obes. 31, 382–384.

Goossens, G.H., Jocken, J.W., Blaak, E.E., Schiffers, P.M., Saris, W.H., van Baak, M.A., 2007b. Endocrine role of the renin–angiotensin system in human adipose tissue and muscle: effect of beta-adrenergic stimulation. Hypertension 49, 542–547.

Goossens, G.H., McQuaid, S.E., Dennis, A.L., van Baak, M.A., Blaak, E.E., Frayn, K.N., Saris, W.H., Karpe, F., 2006. Angiotensin II: a major regulator of subcutaneous adipose tissue blood flow in humans. J. Physiol. 571, 451–460.

Guo, C., Ricchiuti, V., Lian, B.Q., Yao, T.M., Coutinho, P., Romero, J.R., Li, J., Williams, G.H., Adler, G.K., 2008. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. Circulation 117, 2253–2261.

Gupte, M., Boustany-Kari, C.M., Bharadwaj, K., Police, S., Thatcher, S., Gong, M.C., English, V.L., Cassis, L.A., 2008. ACE2 is expressed in mouse adipocytes and regulated by a high-fat diet. Am. J. Physiol. Regul. Integr. Comp. Physiol. 295, R781–R788.

Hainault, I., Nebout, G., Turban, S., Ardouin, B., Ferre, P., Quignard-Boulange, A., 2002. Adipose tissue-specific increase in angiotensinogen expression and secretion in the obese (fa/fa) Zucker rat. Am. J. Physiol. Endocrinol. Metab. 282, E59–66.

Hamdy, O., Porramatikul, S., Al-Ozairi, E., 2006. Metabolic obesity: the paradox between visceral and subcutaneous fat. Curr. Diabetes Rev. 2, 367–373.

Harrison, D., Griendling, K.K., Landmesser, U., Hornig, B., Drexler, H., 2003. Role of oxidative stress in atherosclerosis. Am. J. Cardiol. 91, 7A–11A.

Harte, A.L., McTernan, P.G., McTernan, C.L., Crocker, J., Starcynski, J., Barnett, A.H., Matyka, K., Kumar, S., 2003. Insulin increases angiotensinogen expression in human abdominal subcutaneous adipocytes. Diabetes Obes. Metab. 5, 462–467.

Hayden, M.R., Sowers, K.M., Pulakat, L., Joginpally, T., Krueger, B., Whaley-Connell, A., Sowers, J.R., 2011. Possible mechanisms of local tissue renin–angiotensin system activation in the cardiorenal metabolic syndrome and type 2 diabetes mellitus. Cardiorenal Med. 1, 193–210.

He, Q., Gao, Z.G., Yin, J., Zhang, J., Yun, Z., Ye, J.P., 2011. Regulation of HIF-1 alpha activity in adipose tissue by obesity-associated factors: adipogenesis, insulin, and hypoxia. Am. J. Physiol. Endocrinol. Metab. 300, E877–E885.

Henegar, C., Tordjman, J., Achard, V., Lacasa, D., Cremer, I., Guerre-Millo, M., Poitou, C., Basdevant, A., Stich, V., Viguerie, N., et al., 2008. Adipose tissue transcriptomic signature highlights the pathological relevance of extracellular matrix in human obesity. Genome Biol. 9, R14.

Hosain, G.M.M., Rahman, M., Williams, K.J., Berenson, A.B., 2010. Racial differences in the association between body fat distribution and lipid profiles among reproductive-age women. Diabetes Metab. 36, 278–285.

Hosogai, N., Fukuhara, A., Oshima, K., Miyata, Y., Tanaka, S., Segawa, K., Furukawa, S., Tochino, Y., Komuro, R., Matsuda, M., et al., 2007. Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. Diabetes 56, 901–911.

Hotamisligil, G.S., 2006. Inflammation and metabolic disorders. Nature 444, 860–867.

Iacobellis, G., Petramala, L., Cotesta, D., Pergolini, M., Zinnamosca, L., Cianci, R., De Toma, G., Sciomer, S., Letizia, C., 2010. Adipokines and cardiometabolic profile in primary hyperaldosteronism. J. Clin. Endocrinol. Metab. 95, 2391–2398.

Iwai, M., Horiuchi, M., 2009. Role of renin–angiotensin system in adipose tissue dysfunction. Hypertens. Res. 32, 425–427.

Iwai, M., Tomono, Y., Inaba, S., Kanno, H., Senba, I., Mogi, M., Horiuchi, M., 2009. AT2 receptor deficiency attenuates adipocyte differentiation and decreases adipocyte number in atherosclerotic mice. Am. J. Hypertens. 22, 784–791.

Jain, S., Li, Y., Patil, S., Kumar, A., 2005. A single-nucleotide polymorphism in human angiotensinogen gene is associated with essential hypertension and affects glucocorticoid induced promoter activity. J. Mol. Med. Jmm 83, 121–131.

Jandeleit-Dahm, K.A., Tikellis, C., Reid, C.M., Johnston, C.I., Cooper, M.E., 2005. Why blockade of the renin–angiotensin system reduces the incidence of new-onset diabetes. J. Hypertens. 23, 463–473.

Janke, J., Engeli, S., Gorzelniak, K., Luft, F.C., Sharma, A.M., 2002. Mature adipocytes inhibit in vitro differentiation of human preadipocytes via angiotensin type 1 receptors. Diabetes 51, 1699–1707.

Jayasooriya, A.P., Mathai, M.L., Walker, L.L., Begg, D.P., Denton, D.A., Cameron-Smith, D., Egan, G.F., McKinley, M.J., Rodger, P.D., Sinclair, A.J., et al., 2008. Mice lacking angiotensin-converting enzyme have increased energy expenditure, with reduced fat mass and improved glucose clearance. Proc. Nat. Acad. Sci. USA 105, 6531–6536.

Jones, B.H., Standridge, M.K., Taylor, J.W., Moustaid, N., 1997. Angiotensinogen gene expression in adipose tissue: analysis of obese models and hormonal and nutritional control. Am. J. Physiol. 273, R236–242.

Jonsson, J.R., Game, P.A., Head, R.J., Frewin, D.B., 1994. The expression and localisation of the angiotensin-converting enzyme mRNA in human adipose tissue. Blood Press. 3, 72–75.

Kadowaki, T., Yamauchi, T., Kubota, N., Hara, K., Ueki, K., Tobe, K., 2006. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J. Clin. Invest. 116, 1784–1792.

Kalupahana, N.S., Massiera, F., Quignard-Boulange, A., Ailhaud, G., Voy, B.H., Wasserman, D.H., Moustaid-Moussa, N., 2012. Overproduction of angiotensinogen from adipose tissue induces adipose inflammation, glucose intolerance, and insulin resistance. Obesity (Silver Spring) 20, 48–56.

Karlsson, C., Lindell, K., Ottosson, M., Sjostrom, L., Carlsson, B., Carlsson, L.M., 1998. Human adipose tissue expresses angiotensinogen and enzymes required for its conversion to angiotensin II. J. Clin. Endocrinol. Metab. 83, 3925–3929.

Khan, T., Muise, E.S., Iyengar, P., Wang, Z.V., Chandalia, M., Abate, N., Zhang, B.B., Bonaldo, P., Chua, S., Scherer, P.E., 2009. Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI. Mol. Cell. Biol. 29, 1575–1591.

Kim, S., Soltani-Bejnood, M., Quignard-Boulange, A., Massiera, F., Teboul, M., Ailhaud, G., Kim, J.H., Moustaid-Moussa, N., Voy, B.H., 2006. The adipose renin–angiotensin system modulates systemic markers of insulin sensitivity and activates the intrarenal renin–angiotensin system. J. Biomed. Biotechnol., 27012.

Kouyama, R., Suganami, T., Nishida, J., Tanaka, M., Toyoda, T., Kiso, M., Chiwata, T., Miyamoto, Y., Yoshimasa, Y., Fukamizu, A., et al., 2005. Attenuation of diet-induced weight gain and adiposity through increased energy expenditure in mice lacking angiotensin II type 1a receptor. Endocrinology 146, 3481–3489.

Krskova, K., Filipcik, P., Zilka, N., Olszanecki, R., Korbut, R., Gajdosechova, L., Zorad, S., 2011. Angiotensinogen and angiotensin-converting enzyme mRNA decrease and AT1 receptor mRNA and protein increase in epididymal fat tissue accompany age-induced elevation of adiposity and reductions in expression of GLUT4 and peroxisome proliferator-activated receptor (PPARgamma). J. Physiol. Pharmacol. 62, 403–410.

Krug, A.W., Vleugels, K., Schinner, S., Lamounier-Zepter, V., Ziegler, C.G., Bornstein, S.R., Ehrhart-Bornstein, M., 2007. Human adipocytes induce an ERK1/2 MAP kinases-mediated upregulation of steroidogenic acute regulatory protein (StAR) and an angiotensin II-sensitization in human adrenocortical cells. Int. J. Obes. (Lond.) 31, 1605–1616.

Kurata, A., Nishizawa, H., Kihara, S., Maeda, N., Sonoda, M., Okada, T., Ohashi, K., Hibuse, T., Fujita, K., Yasui, A., et al., 2006. Blockade of Angiotensin II type-1 receptor reduces oxidative stress in adipose tissue and ameliorates adipocytokine dysregulation. Kidney Int. 70, 1717–1724.

Lambert, D.W., Yarski, M., Warner, F.J., Thornhill, P., Parkin, E.T., Smith, A.I., Hooper, N.M., Turner, A.J., 2005. Tumor necrosis factor-alpha convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). J. Biol. Chem. 280, 30113–30119.

Lamounier-Zepter, V., Ehrhart-Bornstein, M., 2006. Fat tissue metabolism and adrenal steroid secretion. Curr. Hypertens. Rep. 8, 30–34.

Lastra, G., Whaley-Connell, A., Manrique, C., Habibi, J., Gutweiler, A.A., Appesh, L., Hayden, M.R., Wei, Y., Ferrario, C., Sowers, J.R., 2008. Low-dose spironolactone reduces reactive oxygen species generation and improves insulin-stimulated glucose transport in skeletal muscle in the TG(mRen2)27 rat. Am. J. Physiol. Endocrinol. Metab. 295, E110–116.

Lee, M.H., Song, H.K., Ko, G.J., Kang, Y.S., Han, S.Y., Han, K.H., Kim, H.K., Han, J.Y., Cha, D.R., 2008. Angiotensin receptor blockers improve insulin resistance in type 2 diabetic rats by modulating adipose tissue. Kidney Int. 74, 890–900.

Lee, R.M., Ding, L., Lu, C., Su, L.Y., Gao, Y.J., 2009. Alteration of perivascular adipose tissue function in angiotensin II-induced hypertension. Can. J. Physiol. Pharmacol. 87, 944–953.

Limor, R., Moataz, U., Knoll, E. and Stern, N., 2012. Aldosterone increases oxidative stress in differentiated but not in undifferentiated 3T3-L1 adipocytes via activation of mineralocorticoid and glucocorticoid receptors. In International Congress of Endocrinology, p Abstract. Florence.

Liu, C., Lv, X.H., Li, H.X., Cao, X., Zhang, F., Wang, L., Yu, M., Yang, J.K., 2011. Angiotensin-(1-7) suppresses oxidative stress and improves glucose uptake via Mas receptor in adipocytes. Acta Diabetol..

Lonnroth, P., Smith, U., 1992. Intermediary metabolism with an emphasis on lipid metabolism, adipose tissue, and fat cell metabolism: a review. In: Bjorntorp, P., Brodoff, B.N. (Eds.), Obesity. Lippincott, Philadelphia, pp 3–14.

Lu, C., Su, L.Y., Lee, R.M., Gao, Y.J., 2010. Mechanisms for perivascular adipose tissue-mediated potentiation of vascular contraction to perivascular neuronal stimulation: the role of adipocyte-derived angiotensin II. Eur. J. Pharmacol. 634, 107–112.

Lu, H., Boustany-Kari, C.M., Daugherty, A., Cassis, L.A., 2007. Angiotensin II increases adipose angiotensinogen expression. Am. J. Physiol. – Endocrinol. Metab. 292, E1280–E1287.

Ma, L.J., Corsa, B.A., Zhou, J., Yang, H., Li, H., Tang, Y.W., Babaev, V.R., Major, A.S., Linton, M.F., Fazio, S., et al., 2011. Angiotensin type 1 receptor modulates macrophage polarization and renal injury in obesity. Am. J. Physiol. Renal. Physiol. 300, F1203–1213.

Mallow, H., Trindl, A., Loffler, G., 2000. Production of angiotensin II receptors type one (AT1) and type two (AT2) during the differentiation of 3T3-L1 preadipocytes. Horm. Metab. Res. 32, 500–503.

Marzolla, V., Armani, A., Zennaro, M.C., Cinti, F., Mammi, C., Fabbri, A., Rosano, G.M., Caprio, M., 2012. The role of the mineralocorticoid receptor in adipocyte biology and fat metabolism. Mol. Cell. Endocrinol. 350, 281–288.

Massiera, F., Bloch-Faure, M., Ceiler, D., Murakami, K., Fukamizu, A., Gasc, J.M., Quignard-Boulange, A., Negrel, R., Ailhaud, G., Seydoux, J., et al. 2001a. Adipose angiotensinogen is involved in adipose tissue growth and blood pressure regulation. FASEB Journal 15 2727-+.

Massiera, F., Seydoux, J., Geloen, A., Quignard-Boulange, A., Turban, S., Saint-Marc, P., Fukamizu, A., Negrel, R., Ailhaud, G., Teboul, M., 2001. Angiotensinogen-deficient mice exhibit impairment of diet-induced weight gain with alteration in adipose tissue development and increased locomotor activity. Endocrinology 142, 5220–5225.

Masuzaki, H., Paterson, J., Shinyama, H., Morton, N.M., Mullins, J.J., Seckl, J.R., Flier, J.S., 2001. A transgenic model of visceral obesity and the metabolic syndrome. Science 294, 2166–2170.

Masuzaki, H., Yamamoto, H., Kenyon, C.J., Elmquist, J.K., Morton, N.M., Paterson, J.M., Shinyama, H., Sharp, M.G.F., Fleming, S., Mullins, J.J., et al., 2003. Transgenic amplification of glucocorticoid action in adipose tissue causes high blood pressure in mice. J. Clin. Investig. 112, 83–90.

Mathai, M.L., Naik, S., Sinclair, A.J., Weisinger, H.S., Weisinger, R.S., 2008. Selective reduction in body fat mass and plasma leptin induced by angiotensin-converting enzyme inhibition in rats. Int. J. Obes. (Lond.) 32, 1576–1584.

Matrozova, J., Steichen, O., Amar, L., Zacharieva, S., Jeunemaitre, X., Plouin, P.F., 2009. Fasting plasma glucose and serum lipids in patients with primary aldosteronism: a controlled cross-sectional study. Hypertension 53, 605–610.

Matsubara, H., 1998. Pathophysiological role of angiotensin II type 2 receptor in cardiovascular and renal diseases. Circ. Res. 83, 1182–1191.

McGehee, R.E., Ron, D., Brasier, A.R., Habener, J.F., 1993. Differentiation-specific element: a cis-acting developmental switch required for the sustained transcriptional expression of the angiotensinogen gene during hormonal-induced differentiation of 3T3-L1 fibroblasts to adipocytes. Mol. Endocrinol. 7, 551–560.

Moan, A., Eide, I.K., Kjeldsen, S.E., 1996. Metabolic and adrenergic characteristics of young men with insulin resistance. Blood Press. Suppl. 1, 30–37.

Munoz, M.C., Giani, J.F., Dominici, F.P., Turyn, D., Toblli, J.E., 2009. Long-term treatment with an angiotensin II receptor blocker decreases adipocyte size and improves insulin signaling in obese Zucker rats. J. Hypertens. 27, 2409–2420.

Nagase, M., Yoshida, S., Shibata, S., Nagase, T., Gotoda, T., Ando, K., Fujita, T., 2006. Enhanced aldosterone signaling in the early nephropathy of rats with metabolic syndrome: possible contribution of fat-derived factors. J. Am. Soc. Nephrol. 17, 3438–3446.

Nguyen, G., 2011. Renin and prorenin receptor in hypertension: what's new? Curr. Hypertens. Rep. 13, 79–85.

Ogihara, T., Asano, T., Ando, K., Chiba, Y., Sakoda, H., Anai, M., Shojima, N., Ono, H., Onishi, Y., Fujishiro, M., et al., 2002. Angiotensin II-induced insulin resistance is associated with enhanced insulin signaling. Hypertension 40, 872–879.

Ozbey, N., Sencer, E., Molvalilar, S., Orhan, Y., 2002. Body fat distribution and cardiovascular disease risk factors in pre- and postmenopausal obese women with similar BMI. Endocr. J. 49, 503–509.

Pan, D.A., Lillioja, S., Kriketos, A.D., Milner, M.R., Baur, L.A., Bogardus, C., Jenkins, A.B., Storlien, L.H., 1997. Skeletal muscle triglyceride levels are inversely related to insulin action. Diabetes 46, 983–988.

Pasarica, M., Gowronska-Kozak, B., Burk, D., Remedios, I., Hymel, D., Gimble, J., Ravussin, E., Bray, G.A., Smith, S.R., 2009a. Adipose tissue collagen VI in obesity. J. Clin. Endocrinol. Metab. 94, 5155–5162.

Pasarica, M., Sereda, O.R., Redman, L.M., Albarado, D.C., Hymel, D.T., Roan, L.E., Rood, J.C., Burk, D.H., Smith, S.R., 2009b. Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. Diabetes 58, 718–725.

Police, S.B., Thatcher, S.E., Charnigo, R., Daugherty, A., Cassis, L.A., 2009. Obesity promotes inflammation in periaortic adipose tissue and angiotensin II-induced abdominal aortic aneurysm formation. Arterioscler. Thromb. Vasc. Biol. 29, 1458- U1123.

Pouliot, M.C., Despres, J.P., Moorjani, S., Lupien, P.J., Tremblay, A., Nadeau, A., Bouchard, C., 1991. Regional variation in adipose tissue lipoprotein lipase activity: association with plasma high density lipoprotein levels. Eur. J. Clin. Invest. 21, 398–405.

Rahmouni, K., Mark, A.L., Haynes, W.G., Sigmund, C.D., 2004. Adipose depot-specific modulation of angiotensinogen gene expression in diet-induced obesity. Am. J. Physiol. Endocrinol. Metab. 286, E891–E895.

Rask, E., Walker, B.R., Soderberg, S., Livingstone, D.E., Eliasson, M., Johnson, O., Andrew, R., Olsson, T., 2002. Tissue-specific changes in peripheral cortisol metabolism in obese women: increased adipose 11beta-hydroxysteroid dehydrogenase type 1 activity. J. Clin. Endocrinol. Metab. 87, 3330–3336.

Rausch, M.E., Weisberg, S., Vardhana, P., Tortoriello, D.V., 2008. Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. Int. J. Obes. 32, 451–463.

Rondinone, C.M., Rodbard, D., Baker, M.E., 1993. Aldosterone stimulated differentiation of mouse 3T3-L1 cells into adipocytes. Endocrinology 132, 2421–2426.

Rosen, E.D., 2005. The transcriptional basis of adipocyte development. Prostaglandins Leukot. Essent Fatty Acids 73, 31–34.

Safonova, I., Aubert, J., Negrel, R., Ailhaud, G., 1997. Regulation by fatty acids of angiotensinogen gene expression in preadipose cells. Biochem. J. 322 (Pt 1), 235–239.

Saiki, A., Koide, N., Watanabe, F., Murano, T., Miyashita, Y., Shirai, K., 2008. Suppression of lipoprotein lipase expression in 3T3-L1 cells by inhibition of adipogenic differentiation through activation of the renin–angiotensin system. Metab. Clin. Exp. 57, 1093–1100.

Saiki, A., Ohira, M., Endo, K., Koide, N., Oyama, T., Murano, T., Miyashita, Y., Shirai, K., 2006. The angiotensin II receptor antagonist valsartan enhances lipoprotein lipase mass in preheparin serum in type 2 diabetes with hypertension. Diabetes Res. Clin. Pract. 74, 242–248.

Santos, R.A.S., e Silva, A.C.S., Maric, C., Silva, D.M.R., Machado, R.P., de Buhr, I., Heringer-Walther, S., Pinheiro, S.V.B., Lopes, M.T., Bader, M., et al., 2003. Angiotensin-(1–7) is an endogenous ligand for the G protein-coupled receptor Mas. Proc. Nat. Acad. Sci. 100, 8258–8263.

Santos, S.H., Fernandes, L.R., Mario, E.G., Ferreira, A.V., Porto, L.C., Alvarez-Leite, J.I., Botion, L.M., Bader, M., Alenina, N., Santos, R.A., 2008. Mas deficiency in FVB/N mice produces marked changes in lipid and glycemic metabolism. Diabetes 57, 340–347.

Saranteas, T., Lolis, E., Mourouzis, C., Potamianou, A., Tesseromatis, C., Varonos, D., 2003. Effect of Losartan on Insulin Plasma Concentrations and LPL Activity in Adipose Tissue of Hypertensive Rats. Horm. Metab. Res. 35 (164), 168.

Sarzani, R., Marcucci, P., Salvi, F., Bordicchia, M., Espinosa, E., Mucci, L., Lorenzetti, B., Minardi, D., Muzzonigro, G., Dessi-Fulgheri, P., et al., 2008a. Angiotensin II stimulates and atrial natriuretic peptide inhibits human visceral adipocyte growth. Int. J. Obes. (Lond.) 32, 259–267.

Sarzani, R., Salvi, F., Dessi-Fulgheri, P., Rappelli, A., 2008b. Renin–angiotensin system, natriuretic peptides, obesity, metabolic syndrome, and hypertension: an integrated view in humans. J. Hypertens. 26, 831–843.

Saye, J.A., Cassis, L.A., Sturgill, T.W., Lynch, K.R., Peach, M.J., 1989. Angiotensinogen gene expression in 3T3-L1 cells. Am. J. Physiol. Cell Physiol. 256, C448–C451.

Sbarbati, A., Osculati, F., Silvagni, D., Benati, D., Galie, M., Camoglio, F.S., Rigotti, G., Maffeis, C., 2006. Obesity and inflammation: evidence for an elementary lesion. Pediatrics 117, 220–223.

Seidell, J.C., Perusse, L., Despres, J.P., Bouchard, C., 2001. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. Am. J. Clin. Nutr. 74, 315–321.

Serazin-Leroy, V., Morot, M., de Mazancourt, P., Giudicelli, Y., 2000. Androgen regulation and site specificity of angiotensinogen gene expression and secretion in rat adipocytes. Am. J. Physiol. – Endocrinol. Metab. 279, E1398–E1405.

Serazin, V., Dieudonné, M.-N., Morot, M., de Mazancourt, P., Giudicelli, Y., 2004. CAMP-positive regulation of angiotensinogen gene expression and protein secretion in rat adipose tissue. Am. J. Physiol. – Endocrinol. Metab. 286, E434–E438.

Sharma, A.M., Janke, J., Gorzelniak, K., Engeli, S., Luft, F.C., 2002. Angiotensin blockade prevents type 2 diabetes by formation of fat cells. Hypertension 40, 609–611.

Shimabukuro, M., Tanaka, H., Shimabukuro, T., 2007. Effects of telmisartan on fat distribution in individuals with the metabolic syndrome. J. Hypertens. 25, 841–848.

Shiuchi, T., Iwai, M., Li, H.S., Wu, L., Min, L.J., Li, J.M., Okumura, M., Cui, T.X., Horiuchi, M., 2004. Angiotensin II type-1 receptor blocker valsartan enhances insulin sensitivity in skeletal muscles of diabetic mice. Hypertension 43, 1003–1010.

Soltis, E.E., Cassis, L.A., 1991. Influence of perivascular adipose tissue on rat aortic smooth muscle responsiveness. Clin. Exp. Hypertens. Part A, Theory and Pract. 13, 277–296.

Stern, N., Osher, E., Greenman, Y., 2007. Hypoadiponectinemia as a marker of adipocyte dysfunction–Part II: The functional significance of low adiponectin secretion. J. Cardiometab. Syndr. 2, 288–294.

Stucchi, P., Cano, V., Ruiz-Gayo, M., Fernandez-Alfonso, M.S., 2009. Aliskiren reduces body-weight gain, adiposity and plasma leptin during diet-induced obesity. Br. J. Pharmacol. 158, 771–778.

Sui, Y., Zhao, H.L., Fan, R.R., Guan, J., He, L., Lee, H.M., Chan, J.C., Tong, P.C., 2010. Renin–angiotensin system activation in renal adipogenesis. Am. J. Physiol. Renal Physiol. 298, F391–400.

Szasz, T., Webb, R.C., 2012. Perivascular adipose tissue: more than just structural support. Clin. Sci. 122, 1–12.

Takahashi, N., Li, F., Hua, K., Deng, J., Wang, C.H., Bowers, R.R., Bartness, T.J., Kim, H.S., Harp, J.B., 2007. Increased energy expenditure, dietary fat wasting, and resistance to diet-induced obesity in mice lacking renin. Cell Metab. 6, 506–512.

Takemori, K., Gao, Y.J., Ding, L., Lu, C., Su, L.Y., An, W.S., Vinson, C., Lee, R.M., 2007. Elevated blood pressure in transgenic lipoatrophic mice and altered vascular function. Hypertension 49, 365–372.

Tam, C., Tordjman, J., Divoux, A., Baur, L.A., Clement, K., 2011. Adipose tissue remodeling in children: the link between collagen deposition and age-related adipocyte growth. Obesity 19, S79.

Tanaka, A., Nomura, Y., Matsuda, A., Ohmori, K., Matsuda, H., 2011. Mast cells function as an alternative modulator of adipogenesis through 15-deoxy-delta-12, 14-prostaglandin J(2). Am. J. Physiol. Cell Physiol. 301, C1360–C1367.

Thatcher, S., Yiannikouris, F., Gupte, M., Cassis, L., 2009. The adipose renin–angiotensin system: role in cardiovascular disease. Mol. Cell. Endocrinol. 302, 111–117.

Tocci, G., Paneni, F., Palano, F., Sciarretta, S., Ferrucci, A., Kurtz, T., Mancia, G., Volpe, M., 2011. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and diabetes: a meta-analysis of placebo-controlled clinical trials. Am. J. Hypertens. 24, 582–590.

Tomono, Y., Iwai, M., Inaba, S., Mogi, M., Horiuchi, M., 2008. Blockade of AT1 receptor improves adipocyte differentiation in atherosclerotic and diabetic models. Am. J. Hypertens. 21, 206–212.

Tondu, A.L., Robichon, C., Yvan-Charvet, L., Donne, N., Le Liepvre, X., Hajduch, E., Ferre, P., Dugail, I., Dagher, G., 2005. Insulin and angiotensin II induce the translocation of scavenger receptor class, type I from intracellular sites to the plasma membrane of adipocytes. J. Biol. Chem. 280, 33536–33540.

Townsend, R.R., 2003. Angiotensin and insulin resistance. Conspiracy theory. Curr. Hypertens. Rep. 5, 110–116.

Tsuchiya, K., Yoshimoto, T., Hirono, Y., Tateno, T., Sugiyama, T., Hirata, Y., 2006. Angiotensin II induces monocyte chemoattractant protein-1 expression via a nuclear factor-kappa B-dependent pathway in rat preadipocytes. Am. J. Physiol. Endocrinol. Metab. 291, E771–E778.

Tuck, M.L., Sowers, J., Dornfeld, L., Kledzik, G., Maxwell, M., 1981. The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. N. Engl. J. Med. 304, 930–933.

Turban, S., Hainault, I., Andre, J., Ferre, P., Quignard-Boulange, A., Guerre-Millo, M., 2001. Molecular and cellular mechanisms of adipose secretion: comparison of leptin and angiotensinogen. J. Cell. Biochem. 82, 666–673.

Vague, J., 1956. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. Am. J. Clin. Nutr. 4, 20–34.

van Harmelen, V., Ariapart, P., Hoffstedt, J., Lundkvist, I., Bringman, S., Arner, P., 2000. Increased adipose angiotensinogen gene expression in human obesity. Obes. Res. 8, 337–341.

Wahrenberg, H., Lonnqvist, F., Arner, P., 1989. Mechanisms underlying regional differences in lipolysis in human adipose tissue. J. Clin. Invest. 84, 458–467.

Wang, B., Jenkins, J.R., Trayhurn, P., 2005. Expression and secretion of inflammation-related adipokines by human adipocytes differentiated in culture: integrated response to TNF-α. American Journal of Physiology - Endocrinology And Metabolism 288, E731–E740.

Weiland, F., Verspohl, E.J., 2008. Variety of angiotensin receptors in 3T3-L1 preadipose cells and differentiated adipocytes. Horm. Metab. Res. 40, 760–766.

Williams, M.J., Hunter, G.R., Kekes-Szabo, T., Snyder, S., Treuth, M.S., 1997. Regional fat distribution in women and risk of cardiovascular disease. Am. J. Clin. Nutr. 65, 855–860.

Xing, Y., Rainey, W.E., Apolzan, J.W., Francone, O.L., Harris, R.B.S., Bollag, W.B., 2012. Adrenal cell aldosterone production is stimulated by very-low-density lipoprotein (VLDL). Endocrinology 153, 721–731.

Yasue, S., Masuzaki, H., Okada, S., Ishii, T., Kozuka, C., Tanaka, T., Fujikura, J., Ebihara, K., Hosoda, K., Katsurada, A., et al., 2010. Adipose tissue-specific regulation of angiotensinogen in obese humans and mice. Impact of nutritional status and adipocyte hypertrophy. Am. J. Hypertens. 23, 425–431.

Ye, J.P., Gao, Z.G., Yin, J., He, Q., 2007. Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. Am. J. Physiol. – Endocrinol. Metab. 293, E1118–E1128.

Ye, Z.W., Wu, X.M., Jiang, J.G., 2009. Expression changes of angiotensin II pathways and bioactive mediators during human preadipocytes-visceral differentiation. Metab. Clin. Exp. 58, 1288–1296.

Yiannikouris, F., Karounos, M., Charnigo, R., English, V.L., Rateri, D.L., Daugherty, A., Cassis, L.A., 2012. Adipocyte-specific deficiency of angiotensinogen decreases plasma angiotensinogen concentration and systolic blood pressure in mice. Am. J. Physiol. Regul. Integr. Comp. Physiol. 302, R244–R251.

Yim, J.-E., Heshka, S., Albu, J.B., Heymsfield, S., Gallagher, D., 2008. Femoral-gluteal subcutaneous and intermuscular adipose tissues have independent and opposing relationships with CVD risk. J. Appl. Physiol. 104, 700–707.

Yokota, T., Oritani, K., Takahashi, I., Ishikawa, J., Matsuyama, A., Ouchi, N., Kihara, S., Funahashi, T., Tenner, A.J., Tomiyama, Y., et al., 2000. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood 96, 1723–1732.

Yvan-Charvet, L., Bobard, A., Bossard, P., Massiera, F., Rousset, X., Ailhaud, G., Teboul, M., Ferre, P., Dagher, G., Quignard-Boulange, A., 2007. In vivo evidence for a role of adipose tissue SR-BI in the nutritional and hormonal regulation of adiposity and cholesterol homeostasis. Arterioscler. Thromb. Vasc. Biol. 27, 1340–1345.

Yvan-Charvet, L., Even, P., Bloch-Faure, M., Guerre-Millo, M., Moustaid-Moussa, N., Ferre, P., Quignard-Boulange, A., 2005. Deletion of the angiotensin type 2 receptor (AT2R) reduces adipose cell size and protects from diet-induced obesity and insulin resistance. Diabetes 54, 991–999.

Yvan-Charvet, L., Massiéra, F., Lamandé, N., Ailhaud, G., Teboul, M., Moustaid-Moussa, N., Gasc, J.-M., Quignard-Boulangé, A., 2009. Deficiency of Angiotensin Type 2 Receptor Rescues Obesity But Not Hypertension Induced by Overexpression of Angiotensinogen in Adipose Tissue. Endocrinology 150, 1421–1428.

Zhang, S., Zhang, X., Yang, L., Yan, Z., Yan, L., Tian, J., Li, X., Song, L., Wang, L., Yang, X., et al., 2012. Increased Susceptibility to Metabolic Syndrome in Adult Offspring of Angiotensin Type 1 Receptor Autoantibody-Positive Rats. Antioxid Redox Signal.

Zheng, J.M., Yao, G.H., Cheng, Z., Wang, R., Liu, Z.H., 2012. Pathogenic role of mast cells in the development of diabetic nephropathy: a study of patients at different stages of the disease. Diabtologia 55, 801–811.

Zhu, Q., Wang, Z., Xia, M., Li, P.L., Van Tassell, B.W., Abbate, A., Dhaduk, R., Li, N., 2011. Silencing of hypoxia-inducible factor-1alpha gene attenuated angiotensin II-induced renal injury in Sprague-Dawley rats. Hypertension 58, 657–664.