Physiology and Pathophysiology of the Adipose Tissue Renin-Angiotensin System

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Abstract—The renin-angiotensin system has long been recognized as an important regulator of systemic blood pressure and renal electrolyte homeostasis, and local renin-angiotensin systems have also been implicated in pathological changes of organ structure and function by modulation of gene expression, growth, fibrosis, and inflammatory response. Recently, substantial data have been accumulated in support of the notion that adipose tissue, besides other endocrine functions, also hosts a local renin-angiotensin system. In the first part of this review, we describe the components of the adipose tissue renin-angiotensin system in human and rodent animal models with respect to regulation of angiotensinogen expression and secretion, formation of angiotensin peptides, and the existence of angiotensin II receptors. In the second part, we describe the role of the adipose tissue renin-angiotensin system in the process of adipogenic differentiation and in the regulation of body weight. We also detail the differential regulation of the adipose tissue renin-angiotensin system in obesity and hypertension and thereby also speculate on its possible role in the development of obesity-associated hypertension. Although some findings on the adipose tissue renin-angiotensin system appear to be confusing, its involvement in the physiology and pathophysiology of adipose tissue has been confirmed by several functional studies. Nevertheless, future studies with more carefully described phenotypes are necessary to conclude whether obesity (by stimulation of adipogenic differentiation) and hypertension are associated with changes of renin-angiotensin system activity in adipose tissue. If so, the physiological relevance of this system in animal models and humans may warrant further interest. **(*Hypertension*. 2000;35:1270-1277.)**

Key Words: adipose tissue ■ angiotensin II ■ hypertension, obesity ■ obesity ■ prostacyclin ■ renin-angiotensin system

The renin-angiotensin system (RAS) has long been recognized as an important regulator of systemic blood pressure and renal electrolyte homeostasis. Over the last decade, several components of the RAS have been detected in a variety of tissues, for example, adrenal gland, kidney, brain, heart, and blood vessels. Consequently, the concept of local RAS as regulators of normal organ function has emerged.[1–3] In addition, local RAS have also been implicated as major players in pathological changes of organ structure and function by modulation of gene expression, growth, fibrosis, and possibly inflammatory response.[4–6] Indeed, the cardiac RAS plays a critical role in the hypertrophic response to pressure load as well as in tissue remodeling after myocardial infarction,[7–10] and the renal RAS has been shown to be involved in fibrotic changes caused by inflammatory and metabolic diseases.[11–14] Consistent with these observations, pharmacological blockade, either by angiotensin-converting enzyme (ACE) inhibitors or type 1 angiotensin-receptor (AT_1) antagonists, is widely used in patients with hypertension, left ventricular hypertrophy, myocardial infarction, congestive heart failure, and diabetic nephropathy.[15–19]

Recently, substantial data have been accumulated in support of the notion that a local RAS is also present in adipose tissue. The occurrence of a local RAS in adipose tissue might appear intriguing, and its physiological meaning thus deserves to be discussed in more detail. In the first part of this article, we review current data on several components of the adipose tissue RAS in human and rodent animal models. In the second part, we describe the involvement of this local RAS in the regulation of adipose tissue physiology and speculate on its possible role in the pathophysiology of obesity and obesity-associated hypertension.

Angiotensinogen Expression and Secretion in Adipose Tissue

Investigation of angiotensinogen (AGT) in adipose tissue began in 1987, when *AGT*-mRNA was found in periaortal brown adipose tissue (BAT) and in cells found within the rat aorta wall.[20] Subsequently, AGT secretion and *AGT*-mRNA were detected in several rat adipose tissue depots and in adipocytes isolated from rat arterial vessel walls, atria, and

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TABLE 1. Angiotensin I–Forming Enzymes in Adipose Tissue and Adipocytes

Models Investigated	REN mRNA	REN Protein	Ang I Formation	Other Enzymes	Inhibition of Ang I Formation
Human	−/+	nd	nd	cathepsin D-	nd
(mature adipocytes)	[25, 26]			mRNA [26]	
Human	+	+	+	nd	nd
(differentiating preadipocytes)	[27]	[27]	[27]		
Rat adipose tissue	−	+	+	nd	+: kallikiren and REN-Ab
(Sprague-Dawley, Wistar)	[47]	[47]	[41, 47]		[47]
Mouse clonal cell lines	−	nd	+	cathepsin D-	−: pepstatin
(3T3-F442A)	[48]		[48]	mRNA [48]	[48]

Ab indicates antibodies; nd, not determined; REN, renin; +, found; and −, not found.

mesenterium.[21–23] In humans, *AGT* expression has been demonstrated in adipose tissue,[24–26] in primary cultured adipocytes,[24,25] and in differentiating preadipocytes.[27] In fact, increasing *AGT* expression and secretion is a characteristic feature of preadipocyte differentiation and is therefore considered a late marker of adipocyte differentiation.[27–32] *Cis* and *trans* regulators of *AGT* expression during adipogenic differentiation have been identified in mouse *3T3-L1* preadipocytes.[33–36]

Fatty acids,[31] glucocorticoids,[32] and possibly tumor necrosis factor-α[37] have been shown to modulate *AGT* expression in *Ob1771* and *3T3-L1* clonal preadipocyte cell lines. In contrast, well-known activators of liver *AGT* expression, such as estrogens, triiodothyronine, and angiotensin II (Ang II), were without effect in *Ob1771* cells,[32] and glucose likewise did not change *AGT* expression in *3T3-L1* cells.[24] Insulin is another important stimulator of liver *AGT* expression, but conflicting results have been obtained on this hormone in adipose tissue: In vivo, streptozotocin-induced insulin deficiency in Sprague-Dawley rats resulted in a fall of adipose tissue *AGT* expression, which was restored by insulin treatment,[38] but insulin did not change *AGT* secretion in primary cultured adipocytes of Obese Zucker rats.[39] Furthermore, insulin stimulated *AGT* expression in *3T3-L1* cells[24] but depressed it in *Ob1771* and *3T3-F442A* cells.[37]

Recent studies with the central-acting sympatholytic agent α-methyl-*p*-tyrosine resulted in decreased adipose tissue *AGT* expression in wild-type mice,[40] implicating the sympathetic nervous system as a stimulator of *AGT*. On the other hand, sympathetic activators such as isoproterenol decreased *AGT* expression in *3T3-L1* cells,[24] and fasting, usually accompanied by sympathetic activation, did not change adipose tissue *AGT* expression in wild-type mice.[40]

In Sprague-Dawley rats, adipose tissue *AGT* expression increased in response to bilateral nephrectomy or treatment with the ACE inhibitor enalapril[21] but was not affected by a sodium-restricted diet.[23] Aging, usually associated with weight gain, resulted in decreased adipose tissue *AGT* expression in Wistar-Kyoto and Wistar Fatty rats but not in Sprague-Dawley and Obese Zucker rats.[41–43] *AGT* expression was higher in visceral than in subcutaneous adipocytes in these rat strains,[42,44] a finding recently also reported in humans.[45,46] Gender differences in *AGT* expression in human adipose tissue are controversial[25,45,46] but have been reported in Sprague-Dawley rats, in which testosterone is a strong activator of adipose tissue *AGT* expression.[44]

Generation of Angiotensin Peptides in Adipose Tissue

Renin activity has been found in rat BAT even after bilateral nephrectomy,[47] and detection of renin-mRNA in human adipocytes[26] and its increase during human preadipocyte differentiation have recently been reported.[27] However, other groups failed to confirm these results (see Table 1 for further details).[25,41,48] Thus, the origin of adipose tissue renin activity remains unsolved. Further studies will be required to determine whether renin is produced by adipocytes, or, as has been reported for other tissues,[49–51] the presence of renin and reninlike activity in adipose tissue is due to uptake of the circulating enzyme. Interestingly, the expression of the renin-binding protein gene has recently been reported in human adipocytes.[25,27] This intracellular localized enzyme[52] is identical to *N*-acyl-D-glucosamine 2-epimerase, usually involved in neuroamine acid metabolism, and apparently functions as a renin inhibitor,[53] leading to a fall in blood pressure when given intravenously.[54] Modulation of renin activity in adipose tissue by this protein therefore appears to be possible.[52]

Consistent with the fact that *AGT* is a late marker of differentiation in mouse and human preadipocytes,[27–32] the production of Ang II has been shown to increase during differentiation of human preadipocytes[27] and can be blocked with the ACE inhibitor captopril in rat adipose tissue.[41] This finding is in agreement with several reports of *ACE* expression and activity in human adipocytes.[25–27,45,55] Stronger *ACE* expression was found in human visceral than in subcutaneous adipose tissue[45]; obesity, on the other hand, was not shown to influence *ACE* expression in humans.[45] Recent studies in human adipose tissue revealed the expression of the Ang I–forming enzyme cathepsin D[26] as well as the Ang II–forming enzymes chymase[25] and cathepsin G.[26] The contribution of these enzymes to the generation of angiotensin peptides in adipose tissue remains to be clearly established, since inhibitors of ACE (ethylenediaminetetraacetic acid, EDTA), chymase (4,2-aminoethyl-benzenesulfonylfluoride, AEBSF), and cathepsin G (pepstatin) did not influence Ang II–forming activity in homogenates of *3T3-F442A* preadipocytes[48] (see Table 2 for further details).

TABLE 2. Angiotensin II–Forming Enzymes in Adipose Tissue and Adipocytes

Models investigated	ACE mRNA	ACE protein	Ang II Formation	Other Enzymes	Influence on Ang II Formation
Human (mature adipocytes)	+ [25, 26, 45, 55]	nd	nd	cathepsin G and chymase-mRNA [25, 26]	nd
Human (differentiating preadipocytes)	+ [27]	+ [27]	+ [27]	nd	nd
Rat adipose tissue (Sprague-Dawley, Wistar)	nd	+ [43]	+ [41, 43]	nd	+: captopril [41]
Mouse clonal cell lines (3T3-F442A)	nd	nd	+ [48]	nd	−: AEBSF, EDTA, trypsin, pepstatin [48]

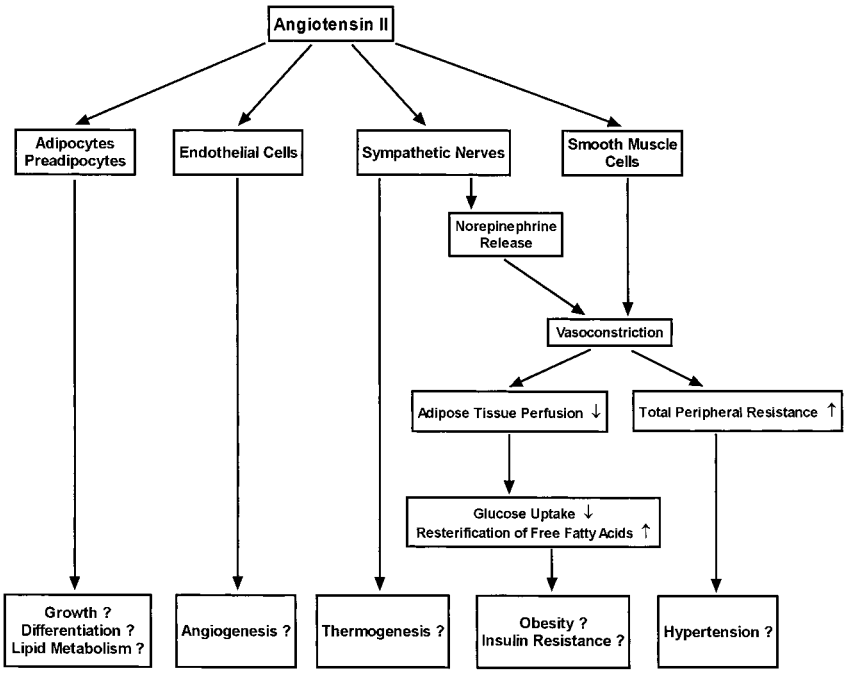
AEBSF indicates 4,2-aminoethyl-benzenesulfonylfluoride; EDTA, ethylenediaminetetra-acetic acid; nd, not determined; +, found, and −, not found.

Presence of Angiotensin Receptors in Adipose Tissue

AT_1 receptors were first identified in 1993 in adipocyte membranes prepared from rat epididymal fat tissue.[56] Since then, evidence on mRNA, protein, and functional levels for AT_1 receptors[25,27,43,57–59] as well as AT_2 receptors[60–62] has been obtained in rodent models and in human adipocytes by several investigators, but the function of these receptors remains to be determined. In vivo, adipose tissue expression of the gene for AT_1 (*AGTR1*) appears to be age-dependent, since old, obese Sprague-Dawley rats had lower AT_1 receptor densities than younger, leaner controls.[43] It has therefore been hypothesized that AT_1 receptor downregulation may be the result of increased adipose tissue formation of Ang II as a result of the development of obesity in older rats. In contrast, long-term treatment of these rats with the specific AT_1 antagonist losartan, which is usually accompanied by increased Ang II plasma and tissue levels, also resulted in downregulation of AT_1 receptors.[43] Obesity did not change adipose tissue AT_1 density in obese Zucker rats[63] but was associated with increased *AGTR1* expression in both visceral and subcutaneous adipose tissue in human subjects, with stronger *AGTR1* expression in visceral adipocytes at any time and any body weight.[45]

Physiological Importance of Adipose Tissue RAS

Adipose tissue not only contains adipocytes but also fibroblast-like cells (eg, preadipocytes), smooth vascular muscle cells, endothelial cells, sympathetic nerve fibers, and mononuclear and lymphocytic cells. The Figure summarizes the possible effects of Ang II on these potential cellular targets in adipose tissue.[4,6,64–66] In addition to the well-known subcutaneous and omental adipose tissue depots, adipocytes can be found in close association to nearly all organs, either as an adipose tissue capsule (eg, kidney, heart, epididymis) or as a fibrous cover containing adipocytes (eg, extima of blood



Hypothetic actions of Ang II in adipose tissue.

vessels). On the basis of the mechanisms proposed in the Figure, it appears reasonable to speculate that Ang II, released by adipocytes, is of potential importance for the physiology and perhaps pathophysiology of adipose tissue and organs in close communication with adipocytes.

Role of RAS in Growth and Differentiation of Adipose Tissue

Ang II acts as a well-recognized growth factor in a variety of tissues and cells,[66–70] and recent data suggest that Ang II may also play a role in adipocyte growth and differentiation.[58,61,71] Stimulation of human preadipocytes with Ang II resulted in an acceleration of the G_1-phase of the cell cycle and increased expression of the cell cycle regulator *cyclin D1*.[58] Furthermore, antisense oligonucleotides directed against the differentiation-specific element binding protein resulted in a dose-dependent inhibition of lipid accumulation in mouse *3T3-L1* preadipocytes.[71] This protein acts as a transactivator by binding to the differentiation-specific element in the *AGT* promoter and thereby initiates *AGT* activation during adipogenic differentiation of the *3T3-L1* clonal cell line.[36]

With respect to preadipocyte differentiation, it is worth noting that prostaglandin I_2 (PGI_2=prostacyclin), which is a major metabolite of arachidonic acid in rodent and human adipose tissue,[72–74] is a potent and specific autocrine effector of adipogenic differentiation.[61,75–79] Interestingly, PGI_2 secretion by adipocytes is induced on exposure to Ang II, both in vitro[61,80] and in the interstitial fluid of rat adipose tissue in vivo.[81] Moreover, Ang II induces in a paracrine manner the differentiation of preadipocytes into adipocytes, as has been demonstrated in coculture experiments of matured *Ob1771* adipocytes with undifferentiated *Ob1771* preadipocytes.[61] In this experimental setting, PGI_2 was secreted exclusively from matured *Ob1771* cells and acted as a chemical relay for the action of Ang II.[61] Consistent with the involvement of PGI_2 as an Ang II–induced paracrine messenger, its adipogenic effect was suppressed by inhibitors of prostaglandin synthesis such as acetyl salicylic acid as well as by neutralizing antibodies against PGI_2.[61] It is of interest to note that evidence of the ability of Ang II to induce rat adipose precursor cells to differentiate ex vivo in adipose tissue explants has recently also been obtained: Immunostaining of a differentiation marker (glycerol-3-phosphate dehydrogenase, GPDH) revealed a decrease of the proportion of undifferentiated GPDH-negative cells on exposure to a stable analogue of PGI_2 or to Ang II, whereas that of differentiating GPDH-positive cells is increased. As expected for an involvement of PGI_2 as a paracrine chemical relay of Ang II, this adipogenic effect of Ang II again is abolished in the presence of acetyl salicylic acid (P. Saint-Marc, C. Darimont, G. Ailhaud, L. Kozak, R. Negrel, unpublished data, 1999).

In the mouse *Ob1771* system, the AT_2-receptor antagonist PD123177 but not the AT_1-receptor antagonist losartan was able to counteract the indirect adipogenic effect of Ang II.[61] Although in contrast, Ang II–induced secretion of prostaglandins from rat adipocytes appears to be mediated by the AT_1 receptor,[43] it can be hypothesized that Ang II, cleaved from AGT secreted by mature adipocytes, may act in a paracrine manner on AT_2 receptors to induce the production and release of PGI_2, thereby promoting adipogenic differentiation in the *Ob1771* model. Nevertheless, the exact profile of action of the different Ang II receptors in the process of adipogenic differentiation appears to depend on the species or models investigated. Schling and Löffler[60] reported upregulation of *AGTR2* expression and downregulation of *AGTR1* expression during in vitro differentiation of human preadipocytes. The authors hypothesize that mitogenic effects of AT_1 receptors in preadipocytes might be replaced by antimitogenic effects of AT_2 receptors in mature adipocytes. However, the same group has recently reported Western blot results that revealed a completely different pattern of Ang II receptor expression in *3T3-L1* cells, in which AT_1 receptors were constantly present, whereas AT_2 receptors apparently disappeared during adipogenic differentiation.[82]

Thus, a balance between AT_1- and AT_2-dependent mechanisms, related to adipocyte hypertrophy and adipose tissue hyperplasia in the various models studied, might be of importance[83] and may be explained by the actual Ang II receptor status. The involvement of AT_2 receptors in preadipocyte differentiation coupled to PGI_2 production[61] and that of AT_1 receptors in the acceleration of the preadipocyte cell cycle[58] as well as the differential pattern of angiotensin-receptor expression in mouse *Ob1771* and *3T3-L1* and human preadipocytes[27,58,60,61,82] clearly indicate that additional experiments are needed to clarify the involvement of the different Ang II–receptor subtypes in these models of various species.

Ang II, Body Weight Regulation, and Adipose Tissue Metabolism

In Sprague-Dawley rats, Ang II infusions resulted in weight loss[84,85] and reduction of white adipose tissue mass.[86] This effect was independent of blood pressure changes and was abolished by losartan.[84] In pair-feeding experiments, 70% of the weight loss was attributable to decreased food intake,[84] whereas other investigators found no changes in food intake but an increased body temperature.[86] Ang II could thus appear as anorexigenic and as an effector of energy expenditure. In contrast, studies in rats and humans have reported weight loss with the administration of ACE inhibitors,[87–89] and age-related white adipose tissue hypertrophy in rats was prevented by the long-term administration of the AT_1 antagonist losartan.[43]

Ang II–associated weight loss[84–86] may be ascribed to an AT_1-dependent lipolytic effect. However, lipolytic activity of Ang II has neither been reported in vitro[61,62,72] nor in vivo.[80] In contrast, in vitro studies demonstrated lipogenic effects of Ang II in *3T3-L1* and human adipocytes, along with increased activity and expression of GPDH and fatty acid synthase.[62] In this later study, receptor binding experiments detected only AT_2 receptors, but Ang II–associated lipogenesis was inhibited by both the AT_2 antagonist PD123319 and the AT_1 antagonist losartan.[62]

Ang II–induced norepinephrine release from BAT in obese Zucker rats is more pronounced in young, preobese rats as compared with older, obese animals.[90] This may result in impaired thermogenesis in older animals and thus may be a mechanism leading to age-associated obesity. Cold exposure

in Sprague-Dawley rats increased Ang II concentrations in plasma and BAT, increased AT_1-receptor density in BAT, and increased norepinephrine release as well as decreased its reuptake in BAT.[91,92] These changes in norepinephrine turnover on cold exposure were completely prevented by treatment with losartan.[91] Thus, cold exposure activates the systemic as well as the local BAT RAS, and this might be a possible mechanism leading to the well-known sympathetic activation in cold-exposed animals. In addition, cold-exposed, pair-fed animals did not show any increase of plasma Ang II levels, meaning that increased food intake, usually seen on cold exposure, appears to be important at least for the systemic activation of the RAS.[92]

Interestingly, 2 recent randomized trials have demonstrated that treatment with the ACE inhibitors captopril (Captopril Prevention Project, CAPPP)[93] or ramipril (Heart Outcomes Prevention Evaluation, HOPE)[94] may reduce the incidence of type 2 diabetes and of diabetes-related end points. Whether or not this effect is related to an effect of ACE inhibition on insulin sensitivity or is mediated by an effect on adipose tissue metabolism remains to be determined.

Regulation of Adipose Tissue RAS in Obesity and Hypertension

A positive relation between AGT plasma levels and blood pressure was first described in 1979 by Walker et al[95] and has since been confirmed not only in humans,[96,97] but also in rat models of hypertension.[98,99] It is further interesting to note that some studies found positive correlations between plasma AGT levels and body mass index in different human populations[100–103] and that linkage between obesity and an *AGT* polymorphism was demonstrated in a genetic isolated population.[104] Not only plasma AGT but also plasma renin activity[45,105,106] and plasma ACE activity[100] were positively correlated to the body mass index in obese human subjects. These findings were not repeated in Obese Zucker rats; however, infusion of Ang II led to a stronger blood pressure increase in obese compared with lean animals.[107]

Besides a significant relation between blood pressure, body mass index, and plasma AGT levels in lean normotensive subjects,[108] we reported that ≈20% of the plasma AGT variance could be explained by plasma leptin levels in this study. Taking plasma leptin as an indicator of adipose tissue mass,[109] this observation might well be explained by a contribution of adipose tissue to AGT plasma levels. However, *AGT* expression was not found to be different in adipose tissue of obese compared with lean and obese hypertensive compared with obese normotensive human subjects in 1 study,[45] but positive correlations have been reported between adipose tissue *AGT* expression and waist-to-hip ratio[46] as well as between AGT secretion by isolated adipocytes and adipocyte volume and body mass index[110] in 2 other studies with obese human subjects. Thus, studies with a greater number of subjects and with better phenotyping are required to determine whether or not there are differences in adipose tissue *AGT* expression between lean and obese as well as normotensive and hypertensive individuals.

AGT expression in adipose tissue has been reported to be regulated in vivo by food intake in Sprague-Dawley rats. Fasting appeared to be accompanied by a reduction of *AGT* expression in adipose tissue and refeeding by an increase.[111] These local changes in *AGT* expression were accompanied by parallel changes in blood pressure, falling on fasting and increasing during refeeding, whereas plasma AGT levels as well as liver *AGT* expression did not change with food intake.[111] Stimulation of adipose tissue *AGT* expression by food intake might be a possible explanation for the refeeding hypertension model. In this rat model of obesity-associated hypertension, high blood pressure usually develops as a result of fasting and refeeding cycles, but to date, sympathetic activation has been the only mechanism examined in this model.[112–115]

It is important to recall that *AGT* expression is positively regulated by fatty acids[31] and carbaprostacyclin[116] by means of a transcriptional mechanism, implicating the peroxisome proliferator–activated receptors PPARδ and/or PPARγ.[117–120] Such a mechanism might be a possible link between *AGT* regulation in adipose tissue, food intake, and the metabolic disturbances accompanying obesity. Nevertheless, no peroxisome proliferator–responsive element has so far been reported within the *AGT* promoter region. *AGT* expression in adipose tissue of animal models of obesity and hypertension as well as in obese and hypertensive subjects has been investigated with positive[42,46,98,99,110,111] and negative results.[24,41,45,121] In that respect, the *AGT*-deficient hypotensive mouse model, which has been generated by homologous recombination,[122] appears as an interesting tool to study adipose tissue cellularity and blood pressure in response to low- or high-fat feeding, as compared with wild-type animals.[123]

Conclusions

Findings on AGT secretion, generation of Ang peptides, and activity of Ang II receptors confirm the existence of a local RAS in adipose tissue. However, available data reveal still unsolved problems. *AGT* gene expression in adipose tissue is subject to differential regulation, but the data are incomplete and sometimes controversial. Formation of Ang peptides has been demonstrated in adipose tissue, but the pathways involved have not been definitely characterized. The presence of both subtypes of Ang II receptors is supported not only by the finding of mRNA or protein but also by ligand-binding as well as functional and pharmacological studies. Nevertheless, the reported patterns of Ang II–receptor subtypes vary substantially between the different models. These inconsistencies may be due to the high number of model organisms and systems that have been investigated. If all species, strains, tissues, and clonal cell lines are considered, the number of models investigated reaches ≈20. In addition, these models not only belong to different species and strains but also represent various stages of adipose cell differentiation, starting with mouse preadipocyte cell lines, which have been investigated during their complete course of differentiation, ending with freshly isolated, mature human adipocytes investigated ex vivo.

Although some findings on the adipose tissue RAS appear to be confusing, its involvement in the physiology and

pathophysiology of adipose tissue has been confirmed by several functional studies. Especially, adipose tissue development and metabolism have been shown to be regulated by Ang II in vitro and in vivo. Nevertheless, the possible contribution of locally produced Ang II on blood pressure regulation still remains to be established. Future studies with carefully described phenotypes are necessary to conclude whether obesity and hypertension are associated with changes of RAS gene expression and activity in adipocytes and, if so, the physiological relevance must be tested in in vivo models. Future studies will also determine whether the local adipose tissue RAS is involved in the beneficial effects of ACE inhibitor treatment on the development of type 2 diabetes, as has been demonstrated by recent randomized cardiovascular prevention trials (CAPPP and HOPE).

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