Published in final edited form as:
Curr Hypertens Rep. 2008 April ; 10(2): 93–98.

Local Adipose Tissue Renin-Angiotensin System

Lisa A. Cassis, PhD, **Sara B. Police, BS**, **Frederique Yiannikouris, PhD**, and **Sean E. Thatcher, PhD**

Abstract

A local renin-angiotensin system (RAS) has been proposed in adipocytes. Adipocytes are a suggested source of components of the RAS, with regulation of their production related to obesity-hypertension. Both angiotensin type 1 and 2 receptors have been localized to adipocytes. Angiotensin II has been demonstrated to regulate adipocyte growth and differentiation, lipid metabolism, and expression and release of adipokines and RAS components, and to promote oxidative stress. Differences in regional expression of RAS components in visceral versus subcutaneous adipose tissue have been suggested as a link between abdominal obesity and cardiovascular disease. Finally, several studies support antihypertensive efficacy of RAS blockade in patients with type 2 diabetes and obesity. Future studies should address the role of adipocyte-specific deficiency of RAS components to definitively determine the relevance of the adipose RAS to normal physiology and to the development of hypertension.

Introduction

Properly functioning adipose tissue is essential to human health, serving as a source of energy during fasting and providing insulation for temperature regulation, among other roles. In the past, adipocytes were recognized as an inert energy source; however, adipocytes are now known to synthesize and secrete proinflammatory factors such as cytokines, acute-phase response proteins, chemotactic/chemoattractants, eicosanoids, prostaglandins, and potentially anti-inflammatory effectors (eg, adiponectin, interleukin [IL]-6, and IL-10) [1]. Collectively, these adipocyte-derived factors have been termed *adipokines* They have increased steadily over the years; more than 50 different adipokines are now known to be secreted from adipocytes. Prominent among adipokines, angiotensinogen and/or angiotensin peptides were identified as secretory products of adipocytes early in the evolution of the dynamic adipocyte, and prior to the current epidemic of obesity in the United States [2,3]. The functional significance of adipocyte production of components of the renin-angiotensin system (RAS) is an area of intense investigation, and may be a link between obesity and cardiovascular disease, including hypertension.

From studying the RAS, several cells and/or tissues have been suggested to possess tissue or local RAS and to generate angiotensin peptides for control of local functions, or to serve as a source for systemic RAS components. The local production of angiotensin II (Ang II) is linked to a variety of diseases, including hypertension, atherosclerosis, and kidney disease. Early studies in rats demonstrated expression of angiotensinogen messenger RNA (mRNA) in brown and white adipose tissue [3,4]. Additional studies demonstrated the presence of each RAS component needed for synthesis and responsiveness to Ang II in rodent and human adipocytes [5]. A variety of studies examined expression of RAS components in adipose tissue in relation to obesity-hypertension. Another area of focus has been differential expression and regulation

Corresponding author: Lisa A. Cassis, PhD, Graduate Center for Nutritional Sciences, Wethington Building, Room 521b, 900 South Limestone Street, University of Kentucky, Lexington, KY 40536-0200, USA. E-mail: E-mail: Icassis@uky.edu.

Disclosures: No potential conflicts of interest relevant to this article were reported.

of RAS components in visceral versus subcutaneous adipose tissue as a link between abdominal obesity and cardiovascular disease. Recent studies have focused on local effects of Ang II on adipocytes, given the presence of both angiotensin type 1 (AT1) and 2 (AT2) receptors on rodent and human adipocytes [5]. Finally, several recent studies support greater efficacy of RAS blockers to treat hypertension and target-organ damage in patients with type 2 diabetes.

Adipocytes as a Source of RAS Components: Relationship to Hypertension

Angiotensinogen, renin or renin-like activity, angiotensin-converting enzyme (ACE), and AT1 and AT2 receptors have been localized to rodent and human adipocytes [5]. Most studies have focused on the regulation of angiotensinogen release from adipocytes as a source for local and/or systemic production of angiotensin peptides. Results from our laboratory demonstrated that angiotensinogen mRNA abundance in adipose tissue was 68% of that in liver, supporting a primary role for adipose angiotensinogen in Ang II production [6••]. Using mice with Ang II receptor deficiencies, study results demonstrated that expression of angiotensinogen in liver, but not in adipose tissue, was reduced in mice with AT1a receptor deficiency [6••]. Studies using AT2 receptor-deficient mice demonstrated that this receptor masked the effects of Ang II to regulate adipose angiotensinogen expression. Accordingly, adipose angiotensinogen expression increased in mice with AT2 receptor deficiency, and this effect was blocked by an AT1 receptor antagonist. Plasma concentrations of angiotensin peptides paralleled liver angiotensinogen expression under normal conditions; however, with AT2 receptor deficiency or in Ang II–infused mice, angiotensinogen expression in adipose tissue more closely paralleled systemic angiotensin peptide concentrations [6••]. In a study that used a different approach to examine the contribution of the adipocyte RAS to the systemic system, hypertensive mice with adipocyte-specific angiotensinogen overexpression exhibited a kidney-specific increase in angiotensinogen expression [7]. These results suggested that the adipocyte RAS extends its physiologic action beyond the local environment of the adipocyte.

An important aspect of adipose-derived production of angiotensinogen and/or angiotensin peptides is their relative contribution to obesity-related hypertension. Studies in obese humans demonstrated that reductions in blood flow through subcutaneous abdominal adipose tissue were associated with increased isoproterenol-mediated release of Ang II [8•,9]. The study authors suggested that enhanced sympathetic nervous system activity with obesity may contribute to obesity-hypertension by increasing adipose production and release of Ang II. Collectively, these findings suggest that with obesity, the adipocyte RAS becomes activated and is a primary contributor to systemic concentrations of angiotensin peptides.

Two recent studies have examined haplotypes of angiotensinogen and their role in driving cell-specific regulation of angiotensinogen, including expression levels in adipocytes. In the 2.1-kilobase pair sequence of the angiotensinogen promoter, the haplotype A (-217) T (-532) A (-793) T (-1074, ATAT) was found to increase promoter activity on transient transfection in preadipocytes and differentiated adipocytes compared with the GCGG haplotype [10]. The variant -217A has been suggested to associate with hypertension in African Americans [11]. Additional studies demonstrated that -20 and -217 polymorphisms of the angiotensinogen promoter have the largest influence on transcription, and that this transcriptional influence of the promoter can influence cell-specific expression, including expression in 3T3-L1 adipocytes [12]. In addition to polymorphisms in the angiotensinogen gene, recent studies suggested that an adenine/cytosine substitution at the nucleotide position (+3126) of the AT2 receptor was associated with small but significant elevation in body mass index in healthy Japanese women [13].

Recent studies demonstrated localization of renin receptors to human adipose tissue [14]. Interestingly, renin receptor expression was shown predominantly in the stromal vascular

fraction of adipose tissue, in a membrane localization. Renin receptor mRNA decreased during stromal vascular cell differentiation, but protein expression was unchanged, suggesting posttranscriptional regulation. Importantly, renin receptor expression was increased in visceral compared with subcutaneous adipose tissue of both lean and obese patients.

In addition to adipose secretion of angiotensinogen, several recent studies have focused on release of angiotensin peptides from adipose tissue. Tissue fragments from periaortic fat of rats were examined for release of angiotensin peptides, and results demonstrated that ACE inhibition did not inhibit Ang II or Ang III production, but did increase tissue generation of several other angiotensin peptides, including angiotensin 1-7 (Ang 1-7) [15]. Moreover, formation of Ang 1-7 prevailed in explants of periaortic fat in comparison with aorta. Our laboratory recently demonstrated expression of ACE2, the monocarboxypeptidase that catabolizes Ang II to form Ang 1-7, in adipocytes [16]. Collectively, these results suggest that adipocytes produce both Ang II and Ang 1-7, and the balance of these peptides may influence local adipocyte function and the systemic RAS.

Effects of Ang II on Adipocytes

Adipocytes express AT1 and AT2 receptors [5]. Thus, locally released angiotensin peptides, or even blood-borne angiotensins, could exert autocrine/paracrine effects to regulate adipocyte functions. With obesity, adipose mass is increased both by adipocyte hypertrophy and through adipocyte differentiation. Several investigators have examined angiotensin effects on adipocyte differentiation, with conflicting results [17-19]. Recent studies examined effects of angiotensins on differentiation of bone marrow-derived stem cells to adipocytes [20••]. Results demonstrated that such differentiation was associated with increased cellular renin and AT2 receptor expression, but reduced angiotensinogen and ACE expression. Ang II inhibited differentiation of mesenchymal stem cells to adipocytes, an effect primarily mediated through AT2 receptors. The authors suggested that the local RAS may negatively regulate adipose mass. However, as mentioned previously, several studies demonstrated the opposite effect of Ang II, including a recent study in which Ang II increased adipocyte differentiation of human preadipocytes isolated from both visceral and perirenal adipose tissue [21]. Further studies, perhaps using mice with adipocyte-specific deficiency of angiotensinogen, are needed to determine whether Ang II increases or decreases adipocyte differentiation.

Inflammation in adipose tissue has been implicated as a link between obesity and the inflammatory-based diseases of diabetes and atherosclerosis [22,23]. Ang II has been demonstrated to promote inflammation through elaboration of chemokines, or through increased oxidative stress [24,25]. In preadipocytes prepared from rat adipose tissue, Ang II increased mRNA and protein for monocyte chemoattractant protein-1 (MCP-1), and Ang II infusion to rats increased mRNA expression of MCP-1 in adipose tissue [26•]. In addition to elaboration of chemokines, blockade of AT1 receptors in mice with diet-induced or genetic obesity reduced the reactive oxygen species originating from adipose tissue [27•]. Collectively, these results suggest that either systemic or locally derived Ang II can influence oxidative stress and inflammation in adipose tissue, thereby contributing to the development of cardiovascular diseases.

A recent study demonstrated that injecting Ang II into wild-type mice reduced circulating high-density lipoprotein (HDL), which was associated with the translocation of scavenger receptor type B1 (SR-B1) proteins to the plasma membrane in adipose tissue [28]. Similar results were obtained in transgenic mice overexpressing angiotensinogen in adipose tissue, raising the possibility that elevations in adipocyte-derived Ang II may contribute to dyslipidemias of obesity through regulation of adipocyte SR-BI and HDL clearance.

Several studies have focused on the effects of RAS blockade in experimental models of obesity. Administration of an AT1 receptor antagonist to type 2 diabetic KK-A^y mice resulted in reduced plasma glucose levels and improved insulin sensitivity [29]. These effects of AT1 receptor blockade were associated with increased glucose uptake in adipose tissue, reduction in adipocyte size, and increased expression of peroxisome proliferator–activated receptor (PPARγ) in adipose tissue. Interestingly, similar findings were demonstrated in rats administered an AT1 receptor antagonist and fed a normal diet [30]. Further studies are required to define whether these effects of AT1 receptor blockade are present in obese humans, and whether they influence obesity-related hypertension.

Regional Differences in RAS Component Expression in Adipose Tissue: Impact on Hypertension

Fat pattern distributions were first described by Vague in 1956, who coined the terms “android” and “gynoid” obesity to describe upper and lower body adiposity, respectively [31]. It has long been held that central, or android, obesity is closely associated with metabolic disturbances, including diabetes and coronary artery disease [31]. Adipose tissue located in the upper, or central, part of the body generally makes up about 20% of total fat. Although subcutaneous adipose is by far the largest adipose depot within the human body, visceral adipose boasts higher metabolic activity, with direct access to the liver via the portal vein [1]. Similarly, human visceral adipose tissue exhibits significantly elevated angiotensinogen mRNA compared with subcutaneous adipose tissue [32]. In patients with the metabolic syndrome, blockade of the AT1 receptor by telmisartan decreased visceral fat area after 24 weeks of treatment, compared with amlodipine [33]. This reduction was associated with enhanced insulin sensitivity. These data suggest local Ang II production by visceral adipocytes may act in a paracrine manner to further facilitate adipose growth and proliferation, and that inhibition of the local adipocyte RAS is worth exploring for therapeutic potential.

The concept that the visceral RAS contributes to blood pressure regulation is evident from studies examining the effect of weight loss—specifically, a decrease in waist circumference—on the adipose RAS and blood pressure. For example, Engeli et al. [34•] examined the effect of weight loss on adipose expression of RAS components and plasma levels of the renin angiotensin-aldosterone system. In this study, obese postmenopausal women who participated in a 13-week weight loss regimen experienced a 5% weight reduction. The weight loss was associated with significantly decreased plasma concentrations of angiotensinogen, renin, and aldosterone, and was accompanied by a 7-mm Hg reduction in systolic blood pressure. Further, the waist circumference reduction was strongly correlated with angiotensinogen expression in subcutaneous abdominal adipose tissue and plasma angiotensinogen levels.

Subcutaneous adipose tissue, the expansive layer of fat located directly beneath the skin's surface, constitutes approximately 80% of total body fat. Although adipose tissue located within the subcutaneous space occupies the majority of adipose content within the body, its metabolic activity is depressed compared with upper body, or visceral adipose tissue. Goossens et al. [9] sought to determine the effect of circulating and locally derived Ang II, and to examine whether Ang II interacts with nitric oxide to regulate adipose tissue blood flow (ATBF). To determine the effect of circulating Ang II on subcutaneous adipose tissue, the ACE inhibitor enalaprilate was infused into the subcutaneous adipose while ATBF was simultaneously monitored. No discernible difference was seen in subcutaneous ATBF between the enalaprilate- and saline-infused patients. However, when subjects were locally infused with the AT1 receptor blocker losartan, ATBF increased markedly compared with saline, suggesting that circulating Ang II reaching the subcutaneous adipose tissue is a negative regulator of ATBF. Further, localized administration of Ang II to human abdominal subcutaneous adipose tissue decreased adipose tissue blood flow in a dose-dependent fashion.

In addition to the generally familiar visceral and subcutaneous adipose, other depots include intraorgan and periorgan adipose, located within or surrounding various organs, respectively. Study results suggest that periorgan adipose maintains a level of metabolic activity between that of subcutaneous and visceral adipose tissue [35,36]. Specifically, periaortic adipose tissue, which is composed of both brown and white adipocytes and encases the length of the aorta, has emerged as a regulator of smooth muscle tone and vascular function. Following the demonstration of angiotensinogen mRNA expression in periaortic adipose tissue by our laboratory [4], we examined the effect of periaortic fat on the contractility of aortic rings [37]. Results demonstrated that contractile responses to electrical stimulation were blunted by an Ang II receptor antagonist, supporting a role for locally derived Ang II as a regulator of smooth muscle responsiveness. Recent studies further demonstrated that the RAS in periaortic adipose tissue can influence Ang II function within the vascular wall. In transgenic lipoatrophic mice that lacked periaortic adipose tissue, blood pressure elevations were attributed to increased AT1 receptor mRNA abundance and enhanced AT1 receptor expression in the aorta, because blood pressure was normalized by an AT1 receptor antagonist [38]. The inability to specifically target RAS components in adipose tissue localized to different anatomic locations has hindered research defining the importance of regional RAS in adipose tissue to cardiovascular control. Moreover, mechanisms for differential expression of RAS components in different adipose depots are unknown. Further research is needed to clarify the significance of regional RAS component expression in adipose tissue, and in the control of blood pressure.

Ang II and Obesity-Hypertension

Given the increasing evidence that an activated adipose RAS exists in obesity, and could potentially contribute to obesity-related hypertension, several studies have examined the effect of RAS blockade in experimental or human obesity-hypertension, and also compared efficacy of RAS inhibition with other antihypertensive agents [39]. Administration of the AT1 receptor antagonist olmesartan to obese KK-A^y mice decreased expression of several proinflammatory cytokines (ie, tumor necrosis factor-α, plasminogen activator inhibitor-1, serum amyloid A, MCP-l) in adipose tissue and reduced adipose reactive oxygen species [27•]. These effects of olmesartan were associated with blood pressure reduction.

In a subanalysis of the Treat to Target Postauthorization Study examining irbesartan to treat hypertension in patients with the metabolic syndrome, patients who were administered irbesartan exhibited a decrease in both systolic and diastolic blood pressure and a reduction in cardiovascular risk factors (decreases in serum triglycerides, fasting blood glucose, and waist circumference, and elevations in HDL cholesterol) [40]. These beneficial effects of irbesartan were more prominent in hypertensive patients with the metabolic syndrome, as compared with hypertensive patients without the metabolic syndrome. The Hypertension-Obesity-Sibutramine study was a prospective study of 171 obese hypertensive patients assigned to a randomized, double-blind, placebo-controlled trial comparing efficacy of one of three different antihypertensive therapies [41••]. After a 2-week run-in period for the antihypertensive therapies, patients received sibutramine as an antiobesity treatment. Results demonstrated that antihypertensive combination therapy with an ACE inhibitor and calcium channel blocker was more advantageous than (β-blocker/diuretic therapy; this combination also supported the weight-reducing actions of sibutramine. In a post-hoc analysis of data from an observational study involving approximately 72,000 hypertensive patients across Germany, all of whom were overweight or obese, the risk factor profile was lower in patients treated with an AT1 receptor antagonist compared with diuretics [42]. These effects of RAS inhibitors, including effects unrelated to their ability to lower blood pressure, have resulted in the recommendation to initiate antihypertensive treatment with an ACE inhibitor in patients with the metabolic syndrome [43].

Conclusions

Adipocytes produce and secrete all components of the RAS (Fig. 1). Thus, the adipocyte can serve as a source of RAS components to the systemic circulation, to adjacent tissues including blood vessels, or locally to control adipocyte growth and differentiation and proinflammatory adipokine expression. Mechanisms for adipocyte RAS activation are not well described, but include nutritional regulation and feedback modulation by Ang II. An understudied area of research relates to the impact of the adipocyte RAS on localized inflammation within adipose tissue and its potential link to obesity-related diseases. Importantly, a dysregulated adipocyte RAS with obesity may contribute to blood pressure elevations by modulating both local and circulating concentrations of RAS components, or by exerting local effects on adipocytes and/or infiltrating macrophages.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Bays H, Rodbard HW, Schorr AB, Gonzalez-Campoy JM. Adiposopathy: treating pathogenic adipose tissue to reduce cardiovascular disease risk. Curr Treat Options Cardiovasc Med 2007;9:259–271. [PubMed: 17761111]

2. Cassis LA, Saye J, Peach MJ. Location and regulation of rat angiotensinogen messenger RNA. Hypertension 1988;11:591–596. [PubMed: 2839415]

3. Campbell DJ, Habener JF. Cellular localization of angiotensinogen gene expression in brown adipose tissue and mesentery: quantification of messenger ribonucleic acid abundance using hybridization in situ. Endocrinology 1987;121:1616–1626. [PubMed: 3665835]

4. Cassis LA, Lynch KR, Peach MJ. Localization of angiotensinogen messenger RNA in rat aorta. Circ Res 1988;62:1259–1262. [PubMed: 3383369]

5. Cassis LA. Fat cell metabolism: insulin, fatty acids, and renin. Curr Hypertens Rep 2000;2:132–138. [PubMed: 10981139]

6••. Lu H, Boustany-Kari CM, Daugherty A, Cassis LA. Angiotensin II increases adipose angiotensinogen expression. Am J Physiol Endocrinol Metab 2007;292:E1280–1287. [PubMed: 17213477]This study examined mechanisms for regulation of the adipocyte RAS, focusing on angiotensin feedback regulation of its synthesis in adipocytes.

7. Kim S, Soltani-Bejnood M, Quignard-Boulange A, et al. The adipose renin-angiotensin system modulates systemic markers of insulin sensitivity and activates the intrarenal renin-angiotensin system. J Biomed Biotecbnol 2006;2006:27012.

8•. Goossens GH, Jocken JW, Blaak EE, et al. Endocrine role of the renin-angiotensin system in human adipose tissue and muscle: effect of beta-adrenergic stimulation. Hypertension 2007;49:542–547. [PubMed: 17224474]This study defined mechanisms for regulation of angiotensin release from human adipose tissue.

9. Goossens GH, McQuaid SE, Dennis AL, et al. Angiotensin II: a major regulator of subcutaneous adipose tissue blood flow in humans. J Physiol 2006;571:451–460. [PubMed: 16396927]

10. Li Y, Jain S, Patil S, Kumar A. A haplotype of angiotensinogen gene that is associated with essential hypertension increases its promoter activity in adipocytes. Vascul Pharmacol 2006;44:29–33. [PubMed: 16303336]

11. Jain S, Tang X, Narayanan CS, et al. Angiotensinogen gene polymorphism at -217 affects basal promoter activity and is associated with hypertension in African-Americans. J Biol Chem 2002;277:36889–36896. [PubMed: 12145290]

12. Dickson ME, Zimmerman MB, Rahmouni K, Sigmund CD. The -20 and -217 promoter variants dominate differential angiotensinogen haplotype regulation in angiotensinogen-expressing cells. Hypertension 2007;49:631–639. [PubMed: 17200439]

13. Kotani K, Sakane N, Saiga K, et al. The uncoupling protein-1 gene -3826A/G polymorphism and hypertension in Japanese subjects. Clin Chem Lab Med 2007;45:1186–1189. [PubMed: 17635070]

14. Achard V, Boullu-Ciocca S, Desbriere R, et al. Renin receptor expression in human adipose tissue. Am J Physiol Regul Integr Comp Physiol 2007;292:R274–R282. [PubMed: 17197644]

15. Bujak-Gizycka B, Madej J, Wolkow PP, et al. Measurement of angiotensin metabolites in organ bath and cell culture experiments by liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS). J Physiol Pharmacol 2007;58:529–540. [PubMed: 17928648]

16. Cassis, L.; Gupte, M.; Boustany, C., et al. Novel expression of ACE2 in adipose tissue and regulation by PPARγ ligands and by high fat diets [abstract CHBRPP142]. Paper presented at the Council for High Blood Pressure Research Conference; San Antonio, TX. October 4−7, 2006;

17. Ailhaud G. Cross talk between adipocytes and their precursors: relationships with adipose tissue development and blood pressure. Ann N Y Acad Sci 1999;892:127–133. [PubMed: 10842658]

18. Brucher R, Cifuentes M, Acuna MJ, et al. Larger anti-adipogenic effect of angiotensin II on omental preadipose cells of obese humans. Obesity (Silver Spring) 2007;15:1643–1646. [PubMed: 17636081]

19. Skurk T, van Harmelen V, Hauner H. Angiotensin II stimulates the release of interleukin-6 and interleukin-8 from cultured human adipocytes by activation of NF-kappaB. Arterioscler Thromb Vasc Biol 2004;24:1199–1203. [PubMed: 15130920]

20••. Matsushita K, Wu Y, Okamoto Y, et al. Local renin angiotensin expression regulates human mesenchymal stem cell differentiation to adipocytes. Hypertension 2006;48:1095–1102. [PubMed: 17060512]This study was the first to examine effects of the adipocyte RAS on differentiation of human mesenchymal stem cells to adipocytes.

21. Sarzani R, Marcucci P, Salvi F, et al. Angiotensin II stimulates and atrial natriuretic peptide inhibits human visceral adipocyte growth. Int J Obes (Lond). 2007Epub ahead of print

22. Weisberg SP, McCann D, Desai M, et al. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796–1808. [PubMed: 14679176]

23. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003;112:1821–1830. [PubMed: 14679177]

24. Daugherty A, Manning MW, Cassis LA. Angiotensin II promotes atherosclerotic lesions and aneurysms in apolipoprotein E-deficient mice. J Clin Invest 2000;105:1605–1612. [PubMed: 10841519]

25. Harrison D, Griendling KK, Landmesser U, et al. Role of oxidative stress in atherosclerosis. Am J Cardiol 2003;91:7A–11A.

26•. Tsuchiya K, Yoshimoto T, Hirono Y, et al. Angiotensin II induces monocyte chemoattractant protein-1 expression via nuclear factor-kappa B-dependent pathway in rat preadipocytes. Am J Physiol Endocrinol Metab 2006;291:E771–E778. [PubMed: 16705055]This study was the first to demonstrate Ang II regulation of chemotactic factors in adipocytes.

27•. Kurata A, Nishizawa H, Kihara S, et al. Blockade of angiotensin II type-1 receptor reduces oxidative stress in adipose tissue and ameliorates adipocytokine dysregulation. Kidney Int 2006;70:1717–1724. [PubMed: 16985520]This study was the first to demonstrate that Ang II promotes generation of reactive oxygen species in adipocytes.

28. Yvan-Charvet L, Bobard A, Bossard P, et al. 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 2007;27:1340–1345. [PubMed: 17363694]

29. Iwai M, Chen R, Imura Y, Horiuchi M. TAK-536, a new AT1 receptor blocker, improves glucose intolerance and adipocyte differentiation. Am J Hypertens 2007;20:579–586. [PubMed: 17485025]

30. Zorad S, Dou JT, Benicky J, et al. Long-term angiotensin II AT1 receptor inhibition produces adipose tissue hypotrophy accompanied by increased expression of adiponectin and PPARgamma. Eur J Pharmacol 2006;552:112–122. [PubMed: 17064684]

31. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. Am J Clin Nutr 1956;4:20–34. [PubMed: 13282851]

32. Giacchetti G, Faloia E, Mariniello B, et al. Overexpression of the renin-angiotensin system in human visceral adipose tissue in normal and overweight subjects. Am J Hypertens 2002;15:381–388. [PubMed: 12022238]

33. Shimabukuro M, Tanaka H, Shimabukuro T. Effects of telmisartan on fat distribution in individuals with the metabolic syndrome. J Hypertens 2007;25:841–848. [PubMed: 17351377]

34•. Engeli S, Bohnke J, Gorzelniak K, et al. Weight loss and the renin-angiotensin-aldosterone system. Hypertension 2005;45:356–362. [PubMed: 15630041]This study was the first to demonstrate that weight loss in humans regulates the adipocyte RAS.

35. Garg A, Fleckenstein JL, Peshock RM, Grundy SM. Peculiar distribution of adipose tissue in patients with congenital generalized lipodystrophy. J Clin Endocrinol Metab 1992;75:358–361. [PubMed: 1639935]

36. Abate N, Garg A. Heterogeneity in adipose tissue metabolism: causes, implications and management of regional adiposity. Prog Lipid Res 1995;34:53–70. [PubMed: 7644553]

37. Soltis EE, Cassis LA. Influence of perivascular adipose tissue on rat aortic smooth muscle responsiveness. Clin Exp Hypertens 1991;13:277–296.

38. Takemori K, Gao YJ, Ding L, et al. Elevated blood pressure in transgenic lipoatrophic mice and altered vascular function. Hypertension 2007;49:365–372. [PubMed: 17200435]

39. Segura J, Ruilope LM. Obesity, essential hypertension and renin-angiotensin system. Public Health Nutr 2007;10:1151–1155. [PubMed: 17903324]

40. Kintscher U, Bramlage P, Paar WD, et al. Irbesartan for the treatment of hypertension in patients with the metabolic syndrome: a sub analysis of the treat to target post-authorization survey. Prospective observational, two armed study in 14,200 patients. Cardiovasc Diabetol 2007;6:12. [PubMed: 17407587]

41••. Scholze J, Grimm E, Herrmann D, et al. Optimal treatment of obesity-related hypertension: the Hypertension-Obesity-Sibutramine (HOS) study. Circulation 2007;115:1991–1998. [PubMed: 17404163]This study showed superior efficacy of an ACE inhibitor to treat obese patients with hypertension.

42. Schindler C, Bramlage P, Thoenes M, et al. Cardiovascular risk in obese hypertensive patients taking various antihypertensive drugs. Clin Drug Investig 2007;27:707–717.

43. Bestermann W, Houston MC, Basile J, et al. Addressing the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome in the southeastern United States, part II: treatment recommendations for management of the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome. Am J Med Sci 2005;329:292–305. [PubMed: 15958871]

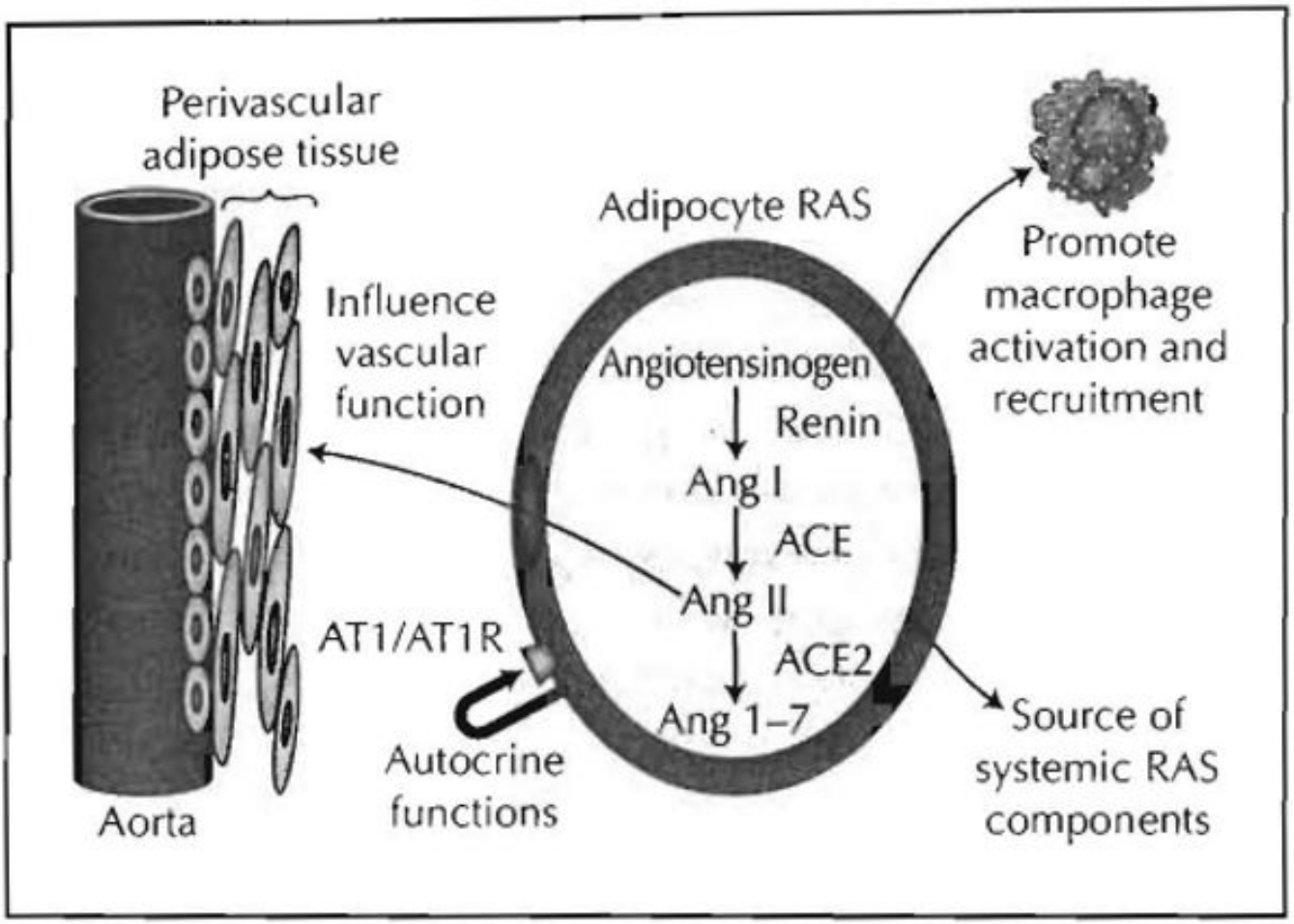

Figure 1.

The adipocyte renin-angiotensin system (RAS) synthesizes and secretes all components of the system for local autocrine/paracrine effects, or as a source for the systemic RAS. The adipocyte RAS can influence local macrophage activation and recruitment to promote inflammation, influence adipocyte growth and differentiation, regulate adipokines, and contribute to the control of vascular tone if localized around blood vessels. ACE—angiotensin-converting enzyme; Ang—angiotensin; AT1—angiotensin type 1; AT1R—AT1 receptor.