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The Link Between Adipose Tissue Renin-Angiotensin-Aldosterone System Signaling and Obesity-Associated Hypertension

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Obese individuals frequently develop hypertension, which is for an important part attributable to renin-angiotensin-aldosterone system (RAAS) overactivity. This review summarizes preclinical and clinical evidence on the involvement of dysfunctional adipose tissue in RAAS activation and on the renal, central, and vascular mechanisms linking RAAS components to obesity-associated hypertension.

Up to 80% of essential hypertension can be ascribed to excess weight via several mechanisms (71, 85). The aim of this paper is to discuss recent insights in how dysfunctional adipose tissue contributes to increased activity of the renin-angiotensin-aldosterone system (RAAS), which is thought to play a crucial role in the pathogenesis of obesity-induced hypertension (51) and whether these insights suggest new antihypertensive strategies.

Adipose Tissue RAAS and Blood Pressure Regulation

Activation of the RAAS is an important mediator of elevated blood pressure under circumstances of obesity. This is not only attributable to sympathetic nervous system overactivity and renal compression (85) but also to dysfunctional adipose tissue.

First, significant angiotensin II (AngII) secretion from abdominal subcutaneous adipose tissue has clearly been demonstrated in obese individuals (87). The fact that the machinery necessary to generate AngII, i.e., angiotensinogen (AGT) mRNA and protein, renin mRNA and activity, and angiotensin converting enzyme (ACE) mRNA and protein, has been encountered in both animal and human adipose tissue (components) (54, 63, 68, 73, 109, 134, 162, 183, 186, 195, 224) indicates that the reported substantial arteriovenous difference in AngII levels is not a consequence of AngII release after reuptake by adipose tissue but of de novo synthesis. This is underlined by observations of AngII production by cultured human adipocytes (187).

Second, white adipose tissue is the most abundant source of AGT after the liver (161), which is particularly relevant in obesity, given the increase in adipose tissue mass and AGT expression in rats with diet-induced obesity, whereas liver AGT expression remains unchanged (23). Subcutaneous adipose tissue AGT expression in obese, compared with lean, humans is enhanced as well, whereas body weight correlates positively and independently with adipose tissue AGT expression (208). How adipose tissue AGT expression relates to AGT secretion is not entirely clear yet, given the fact that unchanged or even decreased adipose tissue AGT expression has been reported as well in both obese animals (74, 203) and humans (53, 56). This could, however, serve as a compensating mechanism for the expanded fat mass, nevertheless resulting in a net increase in AGT release, as observed in obese mice and humans (224).

In obese rats, adipose tissue AGT expression corresponds with plasma AGT and AngII levels and blood pressure (23), whereas both adipose tissue AGT secretion and plasma AGT levels are increased in mice with diet-induced obesity, and adipose-tissue-derived AGT correlates with circulating AGT in these mice before and after weight loss (224). Moreover, mice deficient in adipocyte AGT fed a high-fat diet remain normotensive, whereas wild-type mice fed the same diet display elevations in plasma AngII and blood pressure (225). Correspondingly, in obese, compared with lean, women, plasma AGT, renin, ACE activity, and aldosterone are higher, and decrease after weight loss. Adipose tissue AGT expression is reduced as well following weight loss, and this is correlated with changes in circulating AGT and systolic blood pressure (53).

Third, human adipocytes are also capable of aldosterone production, which is partially AngII dependent (26), and, accordingly, BMI predicts plasma aldosterone concentration in overweight and obese hypertensive patients (171). In addition, adipose-tissue-derived mineralocorticoid-releasing factors, including leptin and complement-C1q TNF-related protein 1 (CTRP1), and also AngII, stimulate aldosterone release in human adrenocortical cells (50, 95, 101). Thus both the adipose

tissue and adrenal glands are sources of aldosterone in obesity.

In addition to local production of AngII and aldosterone or mineralocorticoid-releasing factors, conversion of adipocyte-derived AGT by systemic renin and ACE-activity represents another way in which adipose tissue can contribute to increased circulating levels of AngII and aldosterone (FIGURE 1).

It is not clear whether it is truly adipocyte-derived renin or renin-like activity that is responsible for the generation of AngI and AngII, because renin mRNA levels in human adipocytes are threefold lower compared with human adipocyte AGT levels (55). Due to the presence of cathepsins and chymase in human adipose tissue (54, 109), however, AngI and AngII can be formed via alternative routes. In addition, (pro)renin receptors, which have been encountered in human adipocytes colocalized with renin and seem to be functional (1), may enhance renin enzymatic activity (157), although some investigators report normal AngII levels in rats overexpressing the human (pro)renin receptor (107). Thus it is likely that adipose tissue-derived RAAS components are involved in regulation of blood pressure.

The role of ACE2, angiotensin1–7 (Ang1–7), and the Mas and AT2 receptors, which are thought to constitute a potentially anti-hypertensive axis of the RAAS (179), in obesity-associated hypertension is as yet unclear but seems an important area of investigation. For example, ACE2 deficiency increased systolic blood pressure in mice fed a high-fat diet, probably resulting from decreased metabolism of AngII to Ang1–7 (80), although there are few data in humans.

The RAAS and Obesity-Associated Hypertension: Pathophysiological Mechanisms

Alterations in RAAS activity, in part resulting from dysfunctional adipose tissue as observed in obesity, can interfere with blood pressure regulation at multiple levels.

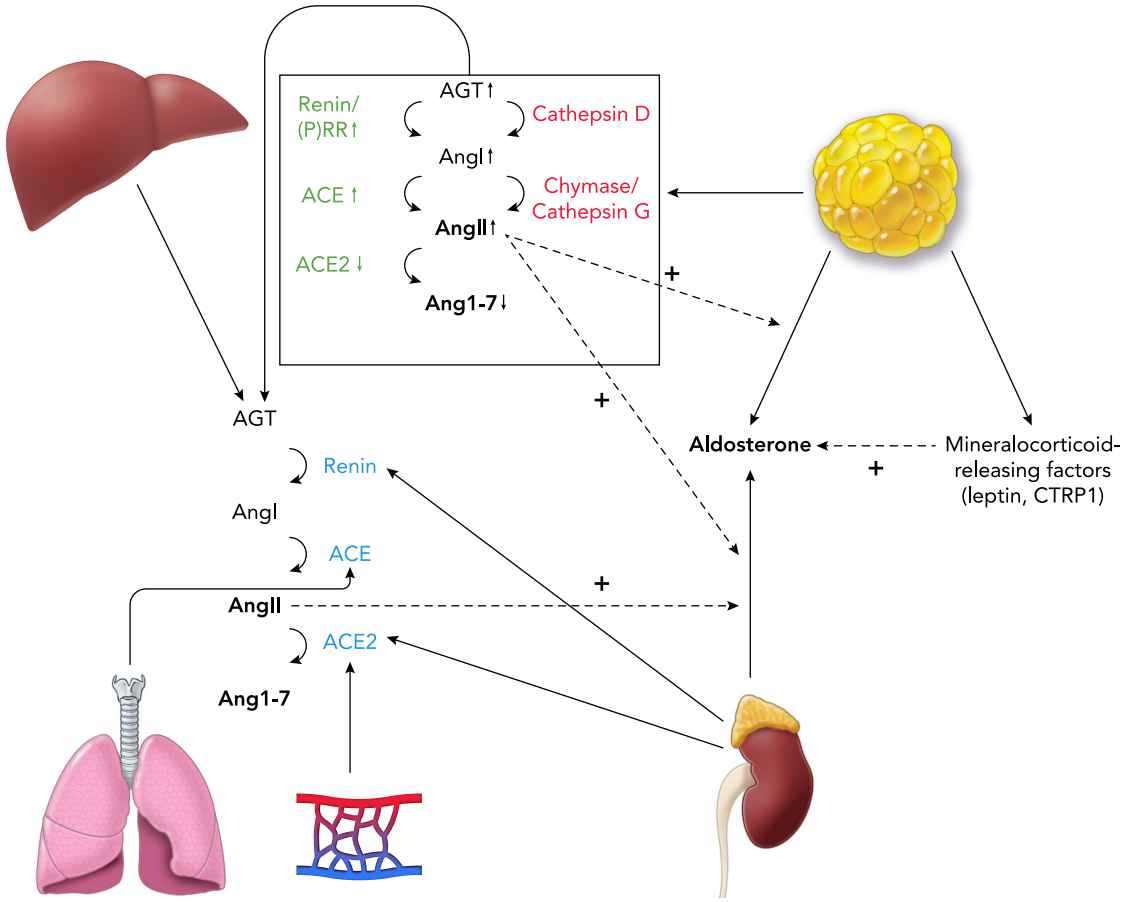

FIGURE 1. **Overview of the adipose tissue RAAS and its interactions with the systemic RAAS**
Adipocyte-derived extracellular RAAS enzymes are indicated in green; intracellular enzymes involved in angiotensin (Ang) I and II generation are indicated in red; and systemic extracellular RAAS enzymes are indicated in blue. AGT, angiotensinogen; Ang1–7, angiotensin1–7; (P)RR, (pro)renin receptor; ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; CTRP1, complement-C1q TNF-related protein 1.

The RAAS and Sodium Homeostasis

Increased renal sodium reabsorption and impaired pressure natriuresis are major contributors to the rise in blood pressure associated with excess weight (85). This is at least partially attributable to increased AngII levels stimulating sodium transport in multiple nephron segments, altering tubuloglomerular feedback and constricting efferent arterioles (13, 28, 36, 83, 84, 113, 160) (FIGURE 2), which may be reinforced by upregulation of the renal AT1R, as has been demonstrated in obese Zucker rats (221). Accordingly, both enalapril and candesartan produced greater increases in urinary sodium excretion in obese compared with lean Zucker rats (202), whereas losartan reduced renovascular resistance in essential hypertensive patients with a relatively high BMI (30). Interestingly, renal AT2R upregulation has been reported as well in obese rats (82), and chronic AT2R activation has been shown to both promote urinary sodium excretion, probably via effects on proximal tubule Na^+-pump activity (4), and lower blood pressure in these rats. Although it remains to be established whether renal AT2R upregulation also occurs in human obesity, these findings may be of therapeutic relevance when AT2R agonists become available for administration in humans.

Increased aldosterone levels combined with a reduced "aldosterone escape" capability constitute another factor partly responsible for the salt surplus in obesity through its actions in the distal nephron promoting sodium reabsorption (38, 65) (FIGURE 2), which are to a lesser extent suppressed by usual regulatory mechanisms in obese rats (169), and potentially by increasing sodium appetite (65) and renal vascular resistance (9, 188).

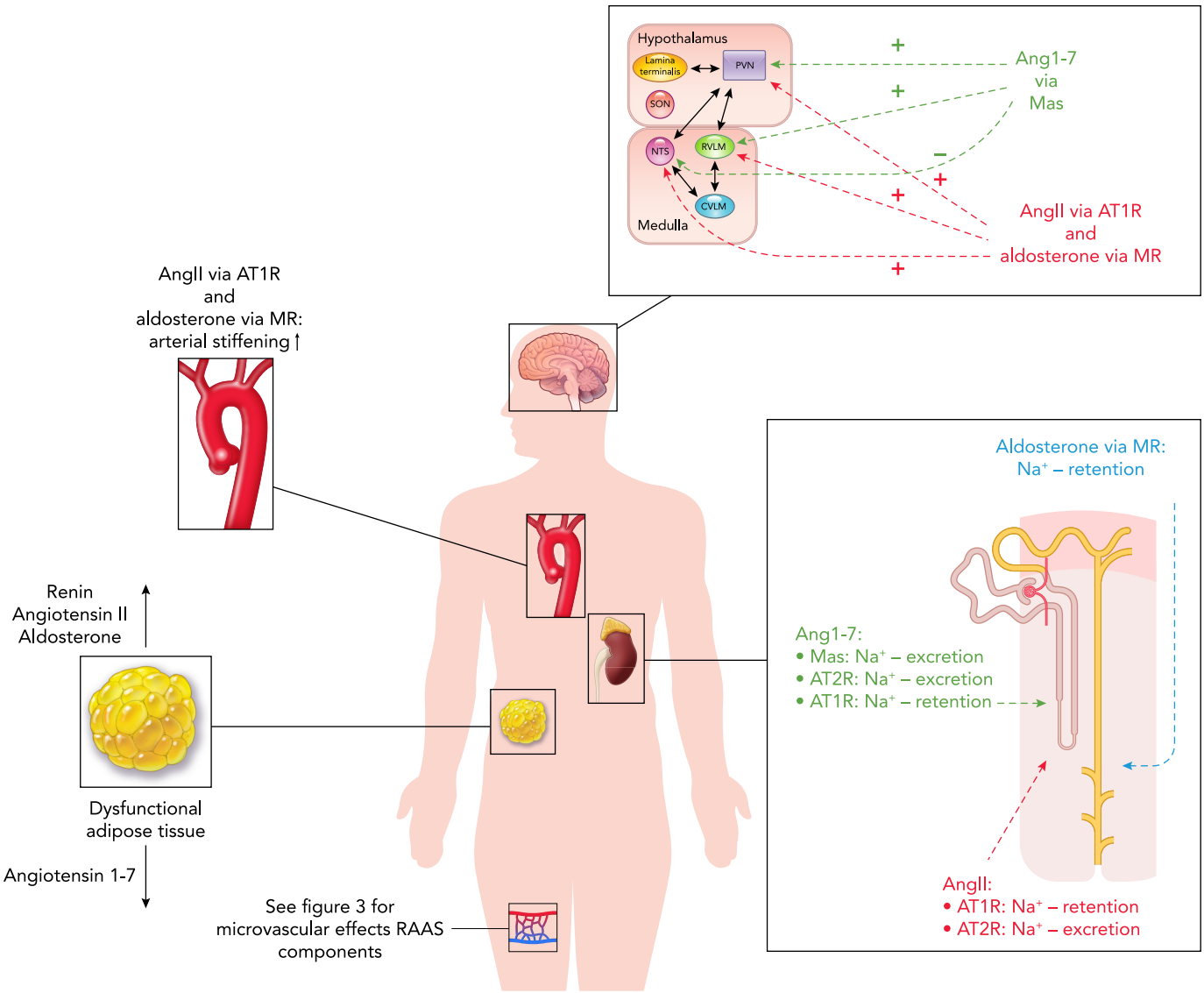

FIGURE 2. **Effects of RAAS components on sodium balance, central blood pressure regulation, and arterial stiffening**
AT1R, AngII type 1 receptor; AT2R, AngII type 2 receptor; MR, mineralocorticoid receptor; SON, supraoptic nucleus; PVN, paraventricular nucleus; NTS, nucleus tractus solitarius; RVLM, rostroventrolateral medulla; CVLM, caudal ventrolateral medulla.

Indeed, mineralocorticoid receptor (MR) blockade with eplerenone reduced sodium retention in parallel with blood pressure in obese, hypertensive dogs (45). Moreover, intracerebral administration of both aldosterone and AngII increased salt appetite in animals, whereas aldosterone enhanced the effect of AngII on sodium intake and vice versa (62, 65). The relevance of these observations for the sodium retention often accompanying human obesity remains to be established. This also applies to the renal vasoconstrictor effects of aldosterone, which may be more pronounced in the left kidney as a result of selectively altered reactivity of the renal vasculature (190).

Intricate interactions exist between Ang1–7 signaling through renal AT1R, AT2R, and Mas receptors, and the net effect of Ang1–7 on sodium balance is ambiguous. Ang1–7 has been demonstrated to reverse the stimulatory effects of AngII on Na^+-ATPase activity in pig kidney proximal tubules by interaction with the Mas receptor (119) and is in addition capable of suppressing proximal tubule Na^+-ATPase through the AT2 receptor (118) and through increasing phosholipase A2 activation (7). On the other hand, Ang1–7 was found to increase Na^+-ATPase activity by binding to the AT1 receptor (120) (FIGURE 2). Inconsistent findings on the renovascular actions of Ang1–7, with potential consequences for sodium balance, have been reported as well in animal models, with Ang1–7 administration exerting either no effect (207), vasodilatation that was prevented by the Mas receptor antagonist A-779 (167, 176), or vasoconstriction (176, 209). These discrepancies are probably due to differences in dose and in degree of RAAS activation (211). Few data are available on the contribution of the renal actions of Ang1–7 to the regulation of blood pressure in healthy, obese, and hypertensive individuals. Nevertheless, findings of decreased urinary Ang1–7 excretion in untreated essential hypertensive individuals (60) and of chronic ACE inhibition being correlated with increases in urinary Ang1–7 levels (135) point to an association of decreased renal Ang1–7 signaling with elevated blood pressure.

The RAAS and the Sympathetic Nervous System

Activation of the sympathetic nervous system (SNS) is an important mechanism linking obesity to hypertension, as illustrated by studies in obese dogs showing that renal denervation induces considerable reductions in blood pressure (90, 132). Alterations in RAAS signaling can partially account for obesity-associated SNS overactivity (51, 85).

Sympathoexcitatory actions of AngII are twofold. Under normal circumstances, AngII does not cross the blood-brain barrier, but circulating AngII is sensed by the subfornical organ (SFO) and area postrema (AP) residing outside the blood-brain barrier, which convey information to key autonomic/neurosecretory centers in the hypothalamus and brain stem, including the paraventricular nucleus of the hypothalamus (PVN), the rostral ventrolateral medulla (RVLM), and the nucleus tractus solitarii (NTS) (5, 59, 198). Elevated circulating AngII levels have been suggested to increase blood-brain barrier permeability (18, 19), thereby allowing for its direct access to these major cardiovascular control centers, which results in increased (renal) sympathetic nerve activity (and thus renin secretion and sodium retention), reduced baroreflex sensitivity, vasopressin release, and elevated mean arterial pressure (10, 22, 126, 129, 201, 213, 227) (FIGURE 2). In addition, AngII facilitates neurotransmission at sympathetic nerve terminals (166). Inhibitory effects of AngII on SNS activity have also been reported (52), potentially resulting from AngII signaling via AT2 receptors in the RVLM (143). The relevance of the latter findings is, however, doubtful, given the fact that increasing peripheral AngII levels generally results in sympathoexcitation, as has been demonstrated in rabbits (149) and normotensive individuals (142). Correspondingly, angiotensin receptor blocker (ARB) treatment was found to reduce sympathetic nerve activity, improve baroreceptor function, and decrease blood pressure in both obese animals and humans (78, 94, 110, 112).

Aldosterone is capable as well of elevating blood pressure by acting directly within the CNS. Brain regions involved in mineralocorticoid modulation of blood pressure are the circumventricular organs, paraventricular and supraoptic nuclei, NTS, and RVLM, and excess aldosterone signaling in these areas is associated with increased sodium appetite, (renal) sympathetic nerve activity, and vasopressin release, impaired baroreflex sensitivity, and elevated blood pressure (72, 77, 153, 226), potentially in part by interaction with AngII (226) (FIGURE 2).

Although the (patho)physiological importance of aldosterone's central effects has been questioned due to its limited blood-brain barrier penetration, a number of findings challenge this concern. In rats, the hypertensive effect of aldosterone or DOCA plus sodium administered subcutaneously was attenuated following intracerebroventricular (ICV) infusion of MR antagonists by reducing sympathetic tone and normalizing baroreflex acitivity (76, 100). Similarly, aldosterone infusion increased muscle sympathetic nerve activity (MSNA) and impaired baroreflex responses in healthy human volunteers (148), whereas spironolactone prevented chlorthalidone-induced sympathetic activation in individuals with untreated *stage 1* hypertension (164). The relative contribution of aldosterone to

obesity-associated sympathoexcitation remains to be determined, but the correlation of aldosterone levels with heart rate variability in obese, diabetic patients with resistant hypertension suggests its involvement (21).

Although central effects of ACE2 generally result in blood pressure reduction (57, 58, 199, 223), the consequences of Ang1–7 signaling for SNS activity and blood pressure depend on the brain region involved (FIGURE 2). Microinjection of Ang1–7 into the RVLM of normotensive and spontaneously hypertensive rats induced stimulation of renal SNA and pressor responses (127), which was blocked by A-779 (61, 152, 178). Similar effects on renal SNA have been observed following A-779 microinjection into the PVN (196), but whether Ang1–7 increases vasopressin release via PVN signaling is as yet unclear (139, 185). On the other hand, when administered ICV or applied directly to the NTS, Ang1–7 increased baroreflex sensitivity and reduced mean arterial pressure and heart rate in both normotensive and hypertensive rats (29, 32), and centrally administered A-779 exerted the opposite effect in different rat models of hypertension (27, 158, 222).

The net effect of CNS Ang1–7 signaling on blood pressure under physiological and pathophysiological circumstances, including hypertension and obesity, remains to be elucidated and confirmed in humans. Findings of increased baroreflex sensitivity and decreased blood pressure following chronic intravenous administration of Ang1–7 in spontaneously hypertensive rats (SHRs) (16), however, suggest that its antihypertensive actions predominate.

The RAAS and Microvascular Function

Microcirculatory (arteriolar and capillary) structure and function determine peripheral vascular resistance and thus blood pressure. Impairment of normal microcirculatory function [i.e., rarefaction, impaired dilatation, and enhanced constriction (103, 108, 124, 125)] is thought to be both cause and consequence of hypertension (40, 49, 88, 103, 191), and is considered an important pathway linking obesity to hypertension (41, 43, 44, 64, 151). An impaired ability of insulin to dilate precapillary terminal arterioles and

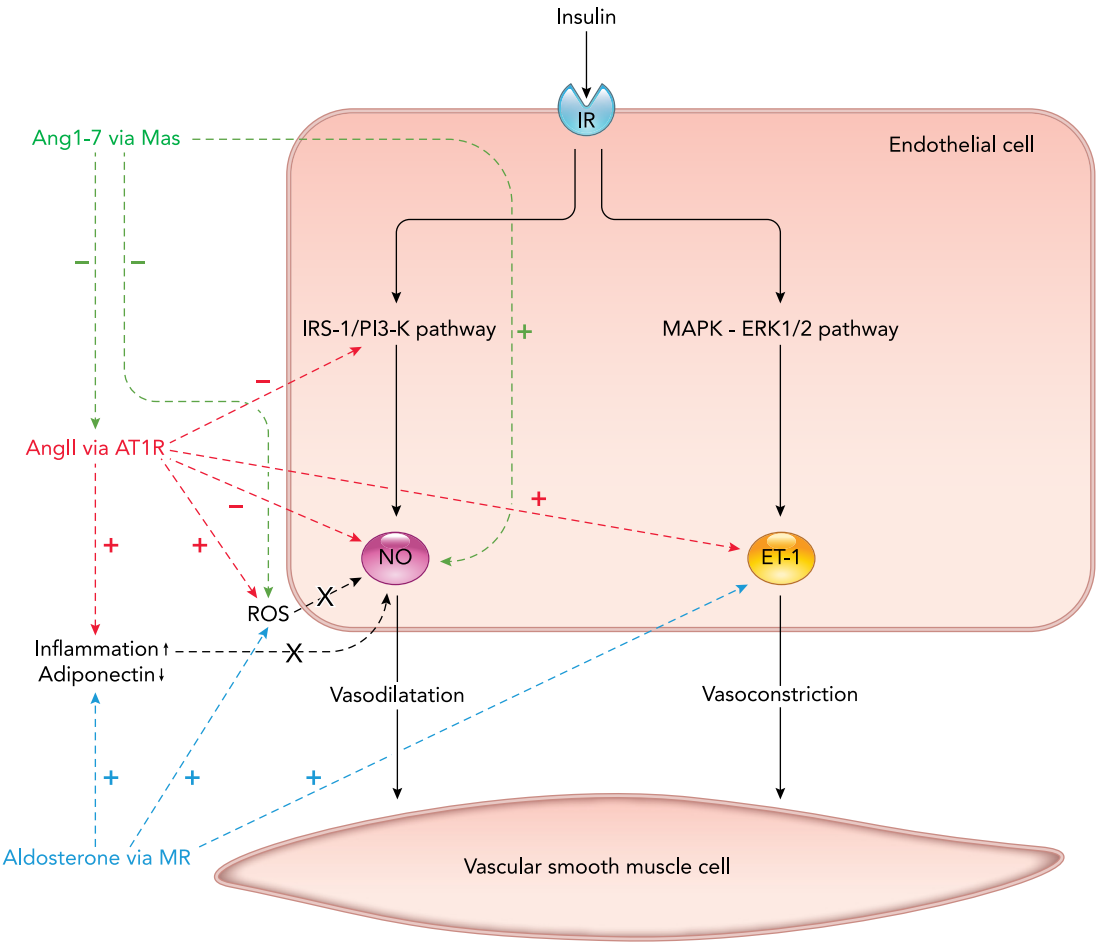

FIGURE 3. **Interference of RAAS components with (insulin-mediated) nitric oxide and endothelin-1 production**
MR, mineralocorticoid receptor; ROS, reactive oxygen species; IR, insulin receptor; NO, nitric oxide; ET-1, endothelin 1.

induce capillary recruitment by increasing endothelial NO synthesis, i.e., microvascular insulin resistance (40, 103, 111, 150) (FIGURE 3), is a feature of obesity-associated microvascular dysfunction that has not only been suggested to increase blood pressure (92, 128) but also to hamper insulin-stimulated glucose uptake in skeletal muscle cells (35, 42, 44, 130, 192–194). Therefore, microvascular insulin resistance may be a shared pathophysiological mechanism between hemodynamic and metabolic consequences of obesity.

Increased AngII levels due to adipose tissue dysfunction can enhance microvascular vasoconstriction through multiple mechanisms via the AT1R (103, 150), notably by decreasing the synthesis and availability of endothelium-derived nitric oxide, stimulating the secretion and action of endothelium-derived vasoconstrictors such as endothelin 1 (ET-1) and prostanoids (25, 33, 103, 150), promoting vascular smooth muscle cell (VSMC) contraction (145), and increasing sympathetic nervous system activity (136) (FIGURE 3).

In addition, AngII interferes with vascular insulin signaling, thereby further hampering NO release (8, 212, 216), and, consequently, insulin-mediated capillary recruitment (105) (FIGURE 3). Thus beneficial effects of ACE-inhibitors and AT1R blockers on insulin-induced microvascular recruitment, as observed in lean and obese rats (34, 215), and healthy and mildly hypertensive individuals (104, 181), might underlie part of their antihypertensive actions and could explain to a certain extent the reduced risk of developing Type 2 diabetes in hypertensive patients following long-term treatment with these agents (6). The vasoactive properties of AngII may comprise more than just vasoconstriction, since it is capable of promoting vasodilatation by increasing NO release and enhancing insulin-mediated muscle microvascular recruitment through the AT2 receptor (31, 150). Increased AT2R protein expression, mediating decreased contractile responses to AngII, has been demonstrated in arteries of obese rats (81), but how these findings fit in the current view of vasoconstriction predominating in obesity (11) or whether this also applies to obese humans is not yet known.

Aldosterone excess in obesity may contribute to a pro-contractile state of the microvasculature (115, 117, 140, 141, 197, 205) by increasing oxidative stress (12, 98, 123), ET-1 release (163), and TNF-α expression, reducing expression of adiponectin (79) and interacting with salt and AngII (99, 144, 197) (FIGURE 3), which could add to its hypertensive effect, as suggested by animal data (46, 156). This might be enhanced by suppression of vascular insulin signaling (91). Accordingly, both MR blockade and endothelium-specific MR deletion improved endothelial function in obese rats and mice (14, 184), whereas low-dose spironolactone increased aortic dilatation in response to insulin in female mice fed a Western diet (48). There are currently no data on microvascular consequences of MR blockade in human obesity. In patients with Type 2 diabetes, however, add-on therapy with spironolactone enhanced coronary microvascular function (70), and in older adults, individual improvements in flow-mediated dilatation (FMD) following eplerenone treatment were associated with higher total body fat (96). Although effects of MR blockade on FMD and (insulin-mediated) microvascular function are not necessarily comparable (69, 97), these findings indicate a favorable response.

Ang1–7 antagonizes microvascular actions of AngII (175) and promotes NO release by activating the Mas, and possibly AT2, receptor (177, 214) (FIGURE 3). This ultimately results in vasorelaxation, as demonstrated in normotensive and obese mice (17, 176), and in normotensive and hypertensive individuals (180, 210). Administration of higher doses of Ang1–7 induced peripheral vasoconstriction in both animals (86, 89, 176) and humans (206), potentially due to concomitant AT1R stimulation and/or Mas receptor saturation and desensitization (75, 209), although the (patho) physiological relevance of these findings is doubtful. Ang1–7 also counteracts the inhibitory effect of AngII on insulin-mediated NO production (204), thereby stimulating insulin-induced muscle microvascular recruitment in rats (66). Vascular actions of Ang1–7 may affect blood pressure, as illustrated by amelioration of hypertension in stroke-prone SHRs following targeted expression of human ACE2 in VSMCs (168), but whether reduced microvascular Ang1–7 signaling contributes to the development of obesity-associated hypertension is currently unknown.

Adipocyte-derived RAAS components act in an endocrine manner to modulate (micro)vascular function, as outlined in the foregoing paragraphs. Paracrine effects have been reported as well, due to the presence of a local fat depot around most of the blood vessels in the human body, termed perivascular adipose tissue (PVAT).

Under normal circumstances, PVAT exerts anticontractile effects (3) that may be mediated for an important part by adipocyte-derived Ang1–7 (122), in addition to adiponectin (220). Moreover, PVAT from lean mice and women was found to enhance insulin-induced vasodilatation and microvascular recruitment, conceivably in an adiponectin-dependent manner (146, 147). In obesity, PVAT-induced anticontractility is diminished or even absent (2), as illustrated by PVAT from obese mice and women, revealing insulin-induced vasoconstriction (146,

147), and this might be related to an imbalance between AngII and Ang1–7 signaling. Indeed, the PVAT anticontractile response could be inhibited with an Ang1–7 antagonist in normotensive rats (133), whereas both AT1R antagonism and ACE inhibition prevented the loss of anticontractile PVAT function in rat small mesenteric arteries subjected to hypoxia (170) and fructose-fed rats (93). Adipocyte-derived aldosterone may also contribute to PVAT-induced contraction through activation of mineralocorticoid receptors. Indeed, eplerenone was found to improve acetylcholine-induced relaxation of small mesenteric arteries containing perivascular fat in obese diabetic mice (26). To our knowledge, studies in humans on the role of RAAS dysregulation in the loss of PVAT anticontractility have not yet been performed.

The RAAS and Arterial Stiffening

Arterial stiffening, which is both a consequence of greater mean arterial pressure and a cause of increased pulse pressure, is commonly observed in obese individuals (47, 121, 172, 200). Therefore, arterial stiffening may also precede elevations in systolic blood pressure and incident hypertension, as has been observed in a diet-induced model of obesity and in Framingham Offspring Study participants (106, 217).

AngII promotes arterial stiffening (FIGURE 2), also independent of effects on blood pressure (165, 219), by enhancing low-grade inflammation, VSMC proliferation, collagen deposition, and the development of fibrosis, which is partly mediated through increased oxidative stress (102, 121, 138, 173). Correspondingly, ACE-inhibitors and ARBs are more potent in reducing arterial stiffening compared with other classes of antihypertensive drugs (24).

Favorable effects of these agents on arterial distensibility, carotid-femoral (cf) and carotid-radial pulse wave velocity (PWV), augmentation index, and central aortic pressure have also been confirmed in obese hypertensive individuals (154, 155), illustrating the significance of AngII-induced vascular remodeling in obesity.

Aldosterone augments arterial stiffening as well (20, 116, 137) (FIGURE 2), through regulation of collagen turnover and fibrous tissue formation, increases in inflammation and oxidative stress (102, 138, 174), and potentially endothelial stiffness (114). These actions may be partly exerted by SMC MRs (67) and are not necessarily blood pressure dependent (189). In addition, aldosterone was found to potentiate some of the hypertrophic effects of AngII on cultured SMCs (174). Thus several measures of arterial stiffening have been demonstrated to improve as a result of MR blockade in hypertensive and obese animals (15, 48, 116), and in essential hypertensive individuals (137, 182, 218), also independent of reductions in blood pressure. Similarly, heart-ankle and brachial-ankle PWV decreased following adrenalectomy in patients with aldosterone-producing adenoma (131). Whether MR blockade affects arterial stiffening in human obesity remains to be established, but the association of aldosterone with heart-femoral PWV in overweight and obese young adults (39) and a reduction of aldosterone levels in parallel with cf-PWV in obese, hypertensive individuals after exercise training (37) suggest a beneficial response.

Although increased arterial stiffness following AngII administration and with aging has been demonstrated in ACE2 knockout murine mesenteric arteries (159), the role of the Ang1–7/Mas axis in the modulation of obesity-related arterial stiffening awaits further investigation.

Conclusions and Future Perspectives

Adipose tissue contributes to increased circulating levels of AngII and aldosterone as observed in obesity, and potentially impairs metabolism of AngII to Ang1–7. Whether adipocyte-derived AGT is predominantly converted to angiotensin peptides within adipose tissue or by systemic RAAS components, and how RAAS dysregulation affects PVAT anticontractility should be further elucidated. Nevertheless, the involvement of adipose tissue in obesity-associated RAAS overactivity stresses the importance of weight loss as antihypertensive strategy in hypertensive obese individuals.

Increased levels of AngII and aldosterone, in part resulting from adipose tissue dysfunction, not only induce sodium retention and sympathoexcitation, but may also impair (insulin-associated) microvascular function and modulate arterial stiffening, ultimately resulting in elevated blood pressure.

By intervening in the regulation of both extracellular volume and vascular tone, ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists can thus be, at least in theory, of great value in the treatment of obesity-associated hypertension. In advanced and long-standing hypertension, the complexity of its pathophysiology increases because of the cardiovascular and renal alterations that are secondary to high blood pressure itself. Multiple agents are then often needed for blood pressure control, which makes it difficult to investigate the relative merits of specific agents. Therefore, whether specific agents such as mineralocorticoid receptor antagonists have superior efficacy in obesity-associated hypertension and can target presumed mechanisms including SNS overactivity, (renal) microvascular dysfunction, and arterial stiffening can probably best be studied in lean and obese

individuals with mild hypertension of relatively short duration, preferably before and after weight loss in the obese individuals. Such studies are very scarce. In addition, unraveling the role of the AT2 receptor in the pathophysiological mechanisms underlying elevated blood pressure in human obesity might be of therapeutic benefit, particularly when AT2R agonists such as Compound 21 become available for clinical applications.

Finally, although the role of angiotensin1–7 in sodium homeostasis and the net influence of its central actions on blood pressure are ambiguous, favorable effects on (insulin-mediated) microvascular function, and potentially vascular stiffening, have been demonstrated. Future research should be directed toward comparing adipocyte ACE2 expression and activity between lean and obese individuals, and before and after weight loss. Moreover, studying the effect of Ang1–7 administration on sodium balance, sympathetic nerve activity, and micro- and macrovascular function in lean vs. obese humans could contribute to a better understanding of its relative contribution to the regulation of extracellular volume and vascular tone. For this latter purpose, Mas receptor agonists and antagonists eligible for administration in humans are also eagerly awaited, and, in addition, Mas receptor agonists may obviously have therapeutic potential. ■

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