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Journal of Renin-Angiotensin-Aldosterone System 2001 2: S114
DOI: 10.1177/14703203010020012001

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What is This?
The renin-angiotensin system in obesity hypertension

Arya M Sharma, Stefan Engeli

Introduction
Increased intra-abdominal fat tissue is an important risk factor for hypertension.1 Development of hypertension in obese individuals is associated with increases in blood volume, heart rate, cardiac output, and cardiac mass.3 Frequently discussed pathogenic mechanisms involved in the development of obesity hypertension include insulin resistance, increased sympathetic nervous system activity, and changes in sodium balance.7,8

Obesity-related changes in kidney function include increased renal blood flow and glomerular filtration rate,9,10 but also increased tubular sodium reabsorption, leading to a rightward shift of the pressure-natriuresis curve.10,11 Intrarenal pressure is significantly increased in obesity, probably by accumulation of intrarenal fat and extracellular matrix.12,13 Sympathetic nerve activity to the kidneys is also enhanced in obesity, with renal norepinephrine spill-over being twice that of lean individuals.22,23 One of the driving forces for sympathetic stimulation appears to be directly related to the central action of the adipose tissue-derived hormone, leptin.24-26 Bilaterally renal-denervated animals do not develop hypertension or sodium retention despite weight gain under a high-fat diet, further illustrating the role of sympathetic renal innervation in obesity-related sodium retention.27,28

The humoral control of sodium balance involves both aldosterone and atrial natriuretic peptide (ANP). As discussed below, aldosterone plasma levels are increased in obesity. Furthermore, ANP plasma levels are decreased29 and the ANP response to a sodium load is significantly blunted in obese subjects.30 Both findings can potentially contribute to obesity-associated sodium retention.31

Expression of the ANP clearance receptor (NPr-C) gene is increased in human adipose tissue of obese hypertensive subjects, but not obese normotensive subjects.33 In rats, fasting selectively inhibits adipose tissue NPr-C gene expression34 and increases circulating ANP levels.32 These findings suggest that increased expression of the NPr-C receptor gene in adipose tissue may directly influence the systemic availability and thus action of natriuretic peptides in obese individuals. Furthermore, the response to exogenous ANP (blood pressure (BP) reduction and natriuresis) in obese hypertensive individuals is significantly enhanced at the end of a low-calorie diet.35 Thus, increased expression of NPr-C in adipose tissue may counteract the protective effects of natriuretic peptides and promote the development of obesity hypertension. Furthermore, down-regulation of the adipocyte NPr-C receptor during weight reduction or fasting might explain the natriuresis observed during the initial phase of a hypocaloric diet.20,32,34

Genetic variants of the RAAS in obesity hypertension
Studies on the relationship between genetic variants of the renin-angiotensin-aldosterone system (RAAS) and obesity hypertension are confounded by the close relationship between RAAS gene variants and BP.35,37 Nevertheless, Hegele et al.38 reported an association between waist-to-hip ratio and the chromosomal region carrying the angiotensinogen (AGT) gene (1q42-43). Furthermore, waist-to-hip ratio, as well as systolic BP, in males was associated with the AGT T174M polymorphism in the same population of Hutterites, a genetically isolated population in North America.A blunted renal vascular response to exogenous angiotensin II (Ang II) was noted in human subjects homozygous for the TT genotype of the AGT M235T polymorphism, and this blunted effect was even more pronounced in obese subjects.39 The AGT M235T variant was also associated with body fat mass and diastolic BP in the highest fat-mass tertile in Canadian women.40 Two promoter variants of the AGT gene have also been associated with anthropometric and BP measures. Thus, subjects with the AA genotype of the AGT A-6G variant responded with a fall in diastolic BP to weight reduction or dietary sodium restriction, whereas other genotypes did not.41 The AGT A-20C promoter variant has also been shown to be closely related to plasma AGT levels as well as to percentage body fat.42 Apart from these findings from association studies on single nucleotide polymorphisms of the RAAS genes, the AGT and angiotensin-converting enzyme (ACE) loci have recently also been linked to obesity hypertension in a genome-wide scan, albeit with rather modest logarithmic odds (LOD) - scores.43 It must however be noted that Cooper et al.44,45 suggested that environmental influences on plasma AGT and plasma ACE levels may be much stronger than genetic influences. Thus, while there is evidence in support of a stimulated systemic RAAS in obesity, the role of genetic factors remains to be determined.
The systemic RAAS is upregulated in obesity

Despite volume expansion and sodium retention, activity of the systemic RAAS appears to be inadver-
tently increased in obese individuals. Thus, several studies report elevated aldosterone levels in obese
individuals compared with lean controls. Interestingly, recent studies implicate an adipocyte-derived factor (presumably a fatty acid) that enhances the release of an aldosterone secre-
tagogue from the liver. Other studies also report positive correlations between plasma AGT levels and plasma ACE activity with increasing body mass index in various human populations. These findings have been replicated in some animal models of obesity, but not in the Obese Zucker rat, where obesity is due to a genetic defect in the leptin receptor. On the other hand, the long-term effects of weight reduction on plasma aldosterone levels and PRA remain contro-
versial. Ang II also increases leptin gene expres-
sion and modulates norepinephrine turnover in brown adipose tissue by an AT1-receptor-mediated mechanism. Apart from a potential role in energy metabolism related to thermogenesis or substrate utilisation, all of these mechanisms may also be important for the regulation of adipose tissue blood flow and may influence BP as well.

Regulation of the adipose tissue RAS in obesity and hypertension

The influence of obesity and hypertension on the expression of the AGT gene in adipose tissue has been addressed by several groups, albeit with conflicting results (Table 1). A potentially important, but as yet unrepeated study in rats, demonstrated that in vivo adipose tissue AGT expression was significantly reduced by fasting and markedly increased by refeeding. These local changes in AGT expression were accompanied by parallel changes in BP with a decrease on fasting and an increase during refeeding, although plasma AGT levels and hepatic AGT expression did not change. Thus, dietary modulation of adipose-tissue AGT expression, apart from its potential role in the development of obesity hypertension, may also play a role in the phenomenon of refeeding.
hypertension found in a rat model of obesity hypertension, where high BP levels usually develop during the course of several fasting and refeeding cycles.90,91

Stimulation of AGT gene expression by tumour necrosis factor α (TNF-α), fatty acids, and glucocorticoids, all of which play a role in obesity, have been reported for Ob1771 mouse clonal preadipocytes.92,93 In light of the hyperinsulinemia that is found in obesity, it is important to recall that insulin is a potent stimulator of hepatic AGT expression.94 However, conflicting results have been reported for this hormone in adipose tissue.95,96,97

Abdominal obese hypertensive subjects are more resistant to insulin’s antilipolytic actions than abdominal obese normotensive or lean normotensive subjects, and thus, free fatty acid release from visceral adipose tissue is increased in obese hypertensives.98 This finding is of importance, as free fatty acids also have an array of vascular actions that may, in concert, contribute to the development of obesity hypertension.99 Interestingly, administration of the ACE-inhibitor (ACE-I) captopril has been shown to augment the ability of insulin to inhibit lipolysis in abdominal obese hypertensive subjects.99 Although this finding may suggest a potential role of Ang II for the regulation of adipocyte metabolism, this effect of ACE-inhibition may also be mediated by an increase in bradykinin.100 This vasoactive peptide can influence the antilipolytic action of insulin, either by stimulating tyrosine-phosphorylation of the insulin receptor and the insulin receptor substrate-1101 or by suppressing lipolysis via bradykinin-stimulated formation of nitric oxide.102,103

The vascular and renal RAAS in obesity

It already has been mentioned that Ang II formed in adipose tissue modulates norepinephrine release and re-uptake.104-106 This explains findings of increased contractile responses of adipose tissue-embedded aortic ring preparations to electrical stimulation compared with ‘denuded’ aortic ring preparations.107 As this effect was prevented by the Ang II receptor antagonist saralasin, it appears to be most likely due to Ang II-stimulated norepinephrine release from adipose tissue. In contrast, adipose tissue-embedded aortic rings were less reactive to norepinephrine stimulation than denuded aortic rings. This effect was abolished by norepinephrine reuptake inhibitors, suggesting norepinephrine uptake by adipose tissue.105 Contractile responses of aortic, but not carotid, rings to Ang II were more pronounced in a dietary model of obese mice and this was abolished by long-term treatment of obese mice with the specific endothelin receptor type A-blocker LU135252.106 Vasomotor reactivity to exogenous Ang II is also increased in Obese Zucker rats in vivo,58 but not in aortic ring preparations from this model in vitro.59 These differences may be attributable to the fact that adipose tissue surrounds blood vessels in the animal, but not in the aortic ring preparations used in this particular study, and the different contractile behaviour may be due to Ang II-related alterations in norepinephrine turnover in denuded vs. adipose-tissue surrounded aortic rings.105

It is worth noting that apart from a potential role of the RAAS in adipose tissue, obesity also appears to affect the renal RAAS. In the above-mentioned dietary model of obese mice, renal ACE activity was significantly increased compared with lean controls.106 Interestingly, concomitant long-term treatment of obese mice with the specific endothelin receptor type A-blocker, LU135252, prevented this increase in renal ACE activity without affecting ACE gene expression.106 This adds to the findings on increased vascular reactivity to Ang II in this animal model of obesity and implicates endothelin-1 as a possible link between obesity and increased activity of tissue RAAS.

Conclusion

Several lines of evidence implicate a role of the RAAS in obesity hypertension. Despite an increased sodium load in obesity, all plasma measures of the RAAS are increased or appear inadequately suppressed. It is of particular relevance that adipose tissue can generate large amounts of Ang II at least within the tissue compartment. Thus, based on the currently available data, we hypothesise that large adipose tissue depots may contribute to plasma AGT levels and that perivascular adipose tissue modulates vascular reactivity (Figure 1). Clearly, further studies will need to clarify the pathogenic role, if any, of the adipose-tissue RAAS in the development of obesity hypertension.
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(including other peptidic systems)

March 2001
Volume 2
Supplement 1
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