A
dipose tissue has classically been assumed to function
simply as a depot storing excess metabolic fuels that can
be mobilized during energy deprivation. It is now well recog-
nized, however, that adipocytes are major players in the regu-
lation of a large number of physiological functions including
blood pressure.1 Among ways, adipocytes influence physi-
ological processes; it is arguably their ability to produce and
secrete hormones that act in a paracrine or endocrine fashion
that has reinvigorated the study of this cell type. For instance,
adipocyte-derived angiotensinogen (AGT), the only known
precursor of angiotensin II (Ang II), is known to contribute
to the circulating pool of this protein.1–6 In the current issue
of Hypertension, Yiannikouris et al7 describe a new way by
which fat can affect the circulating renin-angiotensin system
(RAS) and blood pressure.

The realization that essentially all components of the RAS
are expressed in adipose tissue led to the notion of a local
adipose RAS that may influence metabolism as well as blood
pressure.2 This was further supported by studies in humans
showing positive correlations among fat mass, circulating
AGT, and RAS activity7 that are reversible by weight loss.4
The relevance of the local adipose RAS to blood pressure con-
trol was established using genetically modified animals. For
example, adipocyte tissue-specific transgenic expression of AGT
increases blood pressure in mice.5 Moreover, adipose tissue-
restricted re-expression of AGT in global AGT knockout mice
corrected the low blood pressure.3 Conversely, Yiannikouris et al8
have previously shown that deletion of AGT from adipocytes
resulted in lower systolic blood pressure in C57BL/6 mice
maintained on a normal chow diet. Building on this, in
the current study, Yiannikouris et al7 examined the relevance
of the adipose tissue RAS to the development of obesity-
associated hypertension by assessing the effect of high-fat
diet in mice lacking the AGT gene only in adipose tissue. The
authors found that high-fat diet increased blood pressure in
wild-type mice, but not in adipocyte-specific AGT knockout
animals, demonstrating the importance of adipose tissue AGT
expression for the development of hypertension in obesity
and suggests that the source of systemic RAS activation in
obesity may be derived from adipose tissue expansion. This
seems specific to hypertension because ablation of adipocyte
AGT did not alter the increased heart rate caused by high-fat
feeding.

Interestingly, ablation of AGT from adipocytes did not
alter the weight gain and adiposity caused by high-fat feed-
ing as indicated by similar increase in body weight and fat
mass in conditional knockout mice and controls on high-
fat diet. The impairment in glucose metabolism, which is
commonly associated with obesity, was also reproduced in
mice lacking AGT in adipose tissue arguing that adipocyte
AGT may not be involved in the metabolic disorders caused
by high-fat feeding. Previous studies have shown that RAS
inhibition (either by genetic or pharmacological approach)
reduces adipose tissue mass.6 Conversely, overexpression of
AGT in adipose tissue increased body weight and adiposity.3
Thus, adipocyte-derived AGT may be sufficient, but not
required, for high-fat diet-induced adipose tissue expansion.

The most intriguing finding in the current study relates to
the effect of deleting AGT gene in adipocytes on obesity-
related changes in plasma AGT protein levels. Unexpectedly,
high-fat feeding caused a similar increase in circulating AGT
in wild-type and conditional knockout mice. Previous studies
demonstrated that diet-induced obesity is associated with ele-
vated expression of the AGT gene in several fat pads.9,10 This
has led to the suggestion that an increase in adipose tissue
AGT gene expression may explain the high plasma AGT lev-
els and activation of systemic RAS in obesity. However, the
current study indicates that adipose tissue does not explain
the elevated plasma AGT in obesity. Thus, AGT that account
for systemic RAS activation in obesity may originate from
other tissues. It is important to note, however, that in the cur-
rent study the analysis of adipose tissue AGT gene expression
was limited to 1 white fat pad. Therefore, whether AGT gene
deletion was successful in all fat depots in the conditional
AGT null mice is not clear. If the adipose tissue AGT gene
deletion was not complete, then some of the circulating AGT
may still be from fat.

In contrast to AGT, an increase in plasma Ang II was
detected in high-fat–fed wild-type mice, but not in the
conditional knockout counterparts. These findings highlight
the connection between the local adipose RAS and circulating
RAS and argue for a key role of adipocyte AGT for the
synthesis of circulating Ang II. The importance of adipose
tissue for obesity-related increase in Ang II is further
supported by the demonstration that Ang II levels and renin-
like activity are elevated in the fat explants of obese wild-type
mice, but not in the conditional knockout animals. Together,

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Cross-Talk Enters a New Dimension

Justin L. Grobe, Kamal Rahmouni

See related article, pp 1524–1530
these findings describe a new way by which adipocytes can affect the circulating RAS, specifically through modulation of Ang II synthesis.

The mechanism by which deletion of AGT in adipocytes can have such a profound effect on the production of Ang II and its release to the plasma remains unclear. Several of the enzymes that are required for the conversion of AGT to Ang II such as renin, tonin, cathepsin D, and angiotensin-converting enzyme were found expressed in adipose tissue, but at variable levels. However, none of these enzymes seem to account for the enhanced conversion of AGT to Ang II in obesity or its inhibition in the adipocyte-specific AGT-deficient mice. This raises the possibility that adipocytes may be equipped with other enzymes or mechanisms, which remain to be identified, that synthesize Ang II and are influenced by high-fat feeding. How adipocyte-specific loss of the AGT gene affects such a system and the synthesis of Ang II in adipose tissue remain to be determined. Regardless of the specific mechanisms, however, the determination that increased adipose tissue AGT is required for obesity-induced hypertension supports further the pathophysiological importance of RAS for the cardiovascular disorders associated with obesity. The current study combined with the literature advocates moving RAS inhibition to first-line therapy for human obesity-hypertension.

Sources of Funding
The authors work is supported by National Institutes of Health grants to J.L. Grobe (HL098276) and Dr Rahmouni (HL084207) and from the American Diabetes Association (1-11-BS-127) and the University of Iowa Fraternal Order of Eagles Diabetes Center to Dr Rahmouni.

Disclosures
None.

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The Adipose/Circulating Renin-Angiotensin System Cross-Talk Enters a New Dimension
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Hypertension. 2012;60:1389-1390; originally published online October 29, 2012;
doi: 10.1161/HYPERTENSIONAHA.112.200543

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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