The Adipose/Circulating Renin-Angiotensin System: Cross-Talk Enters a New Dimension

Justin L. Grobe, Kamal Rahmouni

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Adipose 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 recognized, however, that adipocytes are major players in the regulation of a large number of physiological functions including blood pressure. Among ways, adipocytes influence physiological 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. In the current issue of Hypertension, Yiannikouris et al 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. This was further supported by studies in humans showing positive correlations among fat mass, circulating AGT, and RAS activity that are reversible by weight loss. The relevance of the local adipose RAS to blood pressure control was established using genetically modified animals. For example, adipose-tissue-specific transgenic expression of AGT increases blood pressure in mice. Moreover, adipose tissue-restricted re-expression of AGT in global AGT knockout mice corrected the low blood pressure. Conversely, Yiannikouris et al 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 al 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 feeding 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. Conversely, overexpression of AGT in adipose tissue increased body weight and adiposity. Thus, adipose-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 elevated expression of the AGT gene in several fat pads. This has led to the suggestion that an increase in adipose tissue AGT gene expression may explain the high plasma AGT levels 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 current 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,
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.

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References
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