Pathophysiologic role of angiotensin II (AII) type 1 receptor in salt-sensitivity in obesity-related hypertension

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Summary

Given that AII type 1 receptor (Agtr1) is expressed in the adipose tissue, AII may act directly on the adipose tissue. However, whether or not AII modulates directly adipose tissue growth and metabolism *in vivo* and, if so, whether it is mediated via Agtr1 is still a matter of debate. Towards understanding the pathophysiologic role of Agtr1 in salt-sensitivity in obesity-related hypertension, we examined the metabolic phenotypes of mice lacking Agtr1a (*Agtr1a*$^{-/-}$ mice) during a high-fat diet. Using mouse embryonic fibroblasts (MEFs) and primary cultures of mature adipocytes, we also examined the role of Agtr1 in adipocyte differentiation and adipose gene expression *in vitro*. The *Agtr1a*$^{-/-}$ mice exhibited the attenuation of diet-induced body weight gain and adiposity, and insulin resistance relative to wildtype littermates (*Agtr1a*$^{+/+}$ mice). They also showed increased energy expenditure accompanied by sympathetic activation, as revealed by increased rectal temperature and oxygen consumption, increased expression of UCP-1 mRNA in the brown adipose tissue, and increased urinary catecholamine excretion. The tail-cuff systolic blood pressure (BP) of *Agtr1a*$^{-/-}$ mice was significantly lower than that of *Agtr1a*$^{+/+}$ mice ($P < 0.05$). Systolic BP tended to be increased in *Agtr1a*$^{+/+}$ mice fed high-fat diet relative to those fed standard diet. BP was significantly lower in *Agtr1a*$^{-/-}$ mice than in *Agtr1a*$^{+/+}$ mice on a standard diet as reported previously ($P < 0.05$). No significant difference in BP was noted between *Agtr1a*$^{-/-}$ mice fed high-fat diet and those fed standard diet. Using MEFs derived from *Agtr1a*$^{+/+}$ and *Agtr1a*$^{-/-}$ mice, we found no significant difference between genotypes in the capability of differentiating into lipid-laden mature adipocytes. In cultured mature adipocytes, AII increased expression of mRNAs for some adipocytokines, which was abolished by pharmacologic blockade of Agtr1.

This study demonstrates for the first time that *Agtr1a*$^{-/-}$ mice exhibit the attenuation of diet-induced weight gain and adiposity through increased energy expenditure. The data of this study also suggest that AII does not affect directly adipocyte differentiation but can modulate adipocytokine production via Agtr1.