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Role of adipose tissue renin–angiotensin system in metabolic and inflammatory diseases associated with obesity

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Obesity is a leading cause of death worldwide because of its associated inflammatory disorders such as hypertension, cardiovascular and kidney diseases, dyslipidemia, glucose intolerance, and certain types of cancer. Adipose tissue expresses all components of the renin–angiotensin system necessary to generate angiotensin (Ang) peptides for local function. The angiotensin type 1 (AT1) and type 2 (AT2) receptors mediate the effect of Ang II and recent studies have shown that both receptors may modulate fat mass expansion through upregulation of adipose tissue lipogenesis (AT2) and downregulation of lipolysis (AT1). Thus, both receptors may have synergistic and additive effects to promote the storage of lipid in adipose tissue in response to the nutrient environment. The production of angiotensinogen (AGT) by adipose tissue in rodents also contributes to one third of the circulating AGT levels. Increased adipose tissue AGT production in the obese state may be responsible in part for the metabolic and inflammatory disorders associated with obesity. This supports the notion that besides the traditional role of Ang II produced by the liver in the control of blood pressure, Ang II produced by the adipose tissue may more accurately reflect the role of this hormone in the regulation of fat mass and associated disorders.

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Angiotensinogen (AGT), the precursor of the renin–angiotensin system (RAS) is converted through an enzymatic cascade to angiotensin I and angiotensin II (Ang II) by the actions of renin and angiotensin-converting enzyme (ACE), respectively. Ang(1–7) is formed from Ang I and Ang II by ACE2 (Figure 1). The production of Ang II is linked to hypertension and several inflammatory diseases including cardiovascular and kidney diseases, dyslipidemia and glucose intolerance (also known as the metabolic syndrome). AGT is highly expressed in adipose tissue and is constitutively secreted by mature adipocytes from separate adipose depots in animal models and in humans.[1] In rodents, this production may contribute as much as 30% of circulating AGT levels *in vivo*,[2] arguing for a paracrine role of adipose AGT and consistent with the new view of adipose tissue as an endocrine organ. Adipose AGT may also have autocrine effects given that adipose tissue expresses all the components of the RAS, including renin, ACE, and ACE2. This permits local production of Ang II and other angiotensin peptides in adipose tissue.[3,4] Both adipocytes and preadipocytes express angiotensin receptors including Ang II receptors type 1 (AT1) and type 2 (AT2) as well as Ang IV and Ang(1–7) receptors (MasR).[5] This review will summarize the autocrine role of the adipose RAS (aRAS) as well as the critical paracrine role of this system in regulating lipid and glucose homeostasis with consequences on metabolic and inflammatory diseases.

RAS, BODY WEIGHT, AND ENERGY HOMEOSTASIS

RAS and accumulation of body fat

Increased local formation of Ang II in adipose tissue has been originally observed in genetically or diet-induced obese rodents and in humans,[6–8] and generation of transgenic mice overexpressing AGT in adipose tissue leads to the development of obesity.[2] This last observation has been a major contributing factor in favor of Ang II as an endocrine effector in obesity *in vivo*. Our group has also identified that mice lacking AGT or AT2 were protected from high-fat-diet-induced obesity and featured adipose tissue hypotrophy.[9,10]

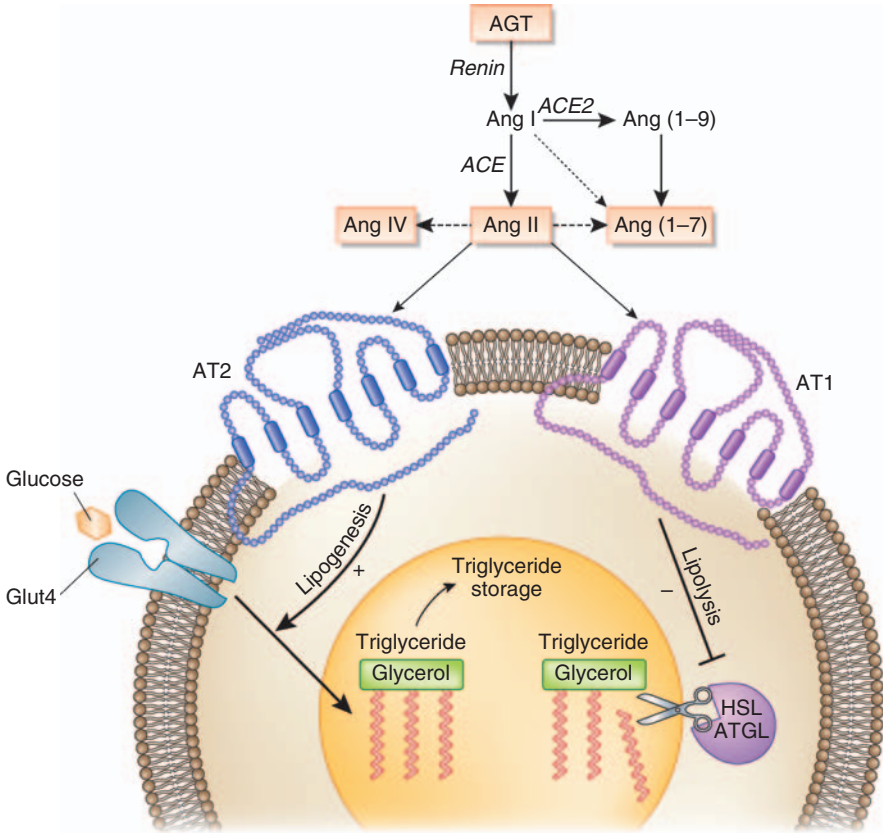

Figure 1 | Formation of angiotensin peptides and roles of AT1 and AT2 receptors in lipid storage capacity of adipocytes. ACE, angiotensin-converting enzyme; AGT, angiotensinogen; Ang, angiotensin; ATGL, adipose triglyceride lipase; Glut, glucose transporter; HSL, hormone-sensitive lipase.

Reports by Kouyama *et al.*,[11] subsequently revealed that mice lacking AT1 were also protected from diet-induced obesity, revealing a synergistic contribution of AT1 and AT2 in mediating the *in vivo* effect of Ang II on adipose tissue development. In contrast to AT1 and AT2 knockout mice, mice lacking the Mas receptor exhibited increased abdominal fat mass associated with higher adipose tissue AGT expression, thereby suggesting a tight regulation of Ang II production by Ang(1–7) in adipose tissue.[12] Recently, studies using knockout mice for renin (with reduction of both Ang II and Ang(1–7) formation) or ACE confirmed that blocking Ang II production in turn prevented fat mass enlargement.[13,14] Similar findings were observed through the use of RAS blockade.[15–17] Together these findings showed an important role for Ang II in the pathogenesis of obesity in rodents.

RAS and energy homeostasis

The reduced fat mass in the aforementioned RAS knockout mouse models was not associated with overall changes in food intake.[9–14] Attempts have been made to establish a link between fat mass and intestinal lipid absorption among the different RAS models. Although Takahashi *et al.* showed that renin-deficient mice exhibited elevated gastrointestinal loss of dietary fat,[13] we and others were not able to find any difference in lipid absorption in AGT or ACE knockout mice.[9,14] By contrast, it is clear that all RAS knockout mouse models tested to date show a higher metabolic rate.[9–14] We previously reported that this increased energy expenditure was the consequence of an increased locomotor activity and whole-body lipid oxidation in AGT- and AT2-deficient mice.[9,10] These findings could be related in part to the regulatory effect of Ang II on adiponectin secretion, which controls muscle fatty acid oxidation capacity.[18,19] Together, these studies suggest that reduced Ang II signaling protects fat mass enlargement in mice by increasing peripheral energy expenditure and whole-body lipid oxidation.

AUTOCRINE ROLE OF THE RAS IN THE REGULATION OF FAT MASS

Role of Ang II in preadipocyte differentiation

Conflicting data exist about the role of Ang II in preadipocyte differentiation *in vitro*,[3,20–22] and little is known about the expression and regulation of AT1, AT2, and MasR in cultured preadipocytes. Because AT2 mRNA expression is known to be under the control of various growth hormones,[23,24] it is possible that the use of dissimilar conditioned media, containing different growth hormones, may account for the