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REVIEWS: CURRECT TOPICS

The renin–angiotensin system in adipose tissue and its metabolic consequences during obesity

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Abstract

Obesity is a worldwide disease that is accompanied by several metabolic abnormalities such as hypertension, hyperglycemia and dyslipidemia. The accelerated adipose tissue growth and fat cell hypertrophy during the onset of obesity precedes adipocyte dysfunction. One of the features of adipocyte dysfunction is dysregulated adipokine secretion, which leads to an imbalance of pro-inflammatory, pro-atherogenic versus anti-inflammatory, insulin-sensitizing adipokines. The production of renin–angiotensin system (RAS) components by adipocytes is exacerbated during obesity, contributing to the systemic RAS and its consequences. Increased adipose tissue RAS has been described in various models of diet-induced obesity (DIO) including fructose and high-fat feeding. Up-regulation of the adipose RAS by DIO promotes inflammation, lipogenesis and reactive oxygen species generation and impairs insulin signaling, all of which worsen the adipose environment. Consequently, the increase of circulating RAS, for which adipose tissue is partially responsible, represents a link between hypertension, insulin resistance in diabetes and inflammation during obesity. However, other nutrients and food components such as soy protein attenuate adipose RAS, decrease adiposity, and improve adipocyte functionality. Here, we review the molecular mechanisms by which adipose RAS modulates systemic RAS and how it is enhanced in obesity, which will explain the simultaneous development of metabolic syndrome alterations. Finally, dietary interventions that prevent obesity and adipocyte dysfunction will maintain normal RAS concentrations and effects, thus preventing metabolic diseases that are associated with RAS enhancement.

Keywords: Adipose tissue; Renin–angiotensin system; Diet; Adipocyte; Hypertension; Diabetes

1. The classical renin–angiotensin system (RAS)

The enzymatic function of renin was established in 1898 by Tigerstedt and Bergman. Since then, the RAS has been extensively studied, and various hormones and receptors are now recognized as players in this system [1]. Therefore, multiple effects of the system and its regulation at cellular and systemic levels have been described. Because regulation of the RAS influences several levels, every level should be independently regulated in harmony with other systems to maintain homeostasis. The RAS system produces angiotensin II (Ang II) from angiotensin I (Ang I) and angiotensinogen (AGT) via renin and angiotensin-converting enzyme (ACE). In the classical pathway, AGT is produced mainly by the liver and is drained to the circulation. Subsequently, AGT is converted into the biologically inactive peptide Ang I through the action of renin, which is also released into the bloodstream. Renin is an aspartyl protease that is primarily produced by juxtaglomerular cells in the renal afferent arteriole as preprorenin, which is converted to prorenin and then to active renin [2,3]. This enzyme cleaves AGT to release the N-terminal decapeptide Ang I [4]. Then ACE, a peptidyldipeptide hydrolase located in vascular endothelial cells, separates the C-terminal dipeptide from angiotensin I to produce the octapeptide Ang II [5]. Additionally, ACE metabolizes the vasodilator bradykinin and inactivates it [6]. For these reasons, ACE has a dual role of increasing vasoconstriction and inactivating vasodilation.

The main effector hormone of the system is Ang II, which binds to the Ang II type 1 (AT1), and Ang II type 2 (AT2) G-protein coupled receptors to exert its biological functions. AT1 interacts with multiple heterotrimeric G proteins to produce second messengers such as inositol trisphosphate, diacylglycerol and reactive oxygen species [7]. Although other roles have been described for Ang II, most of the pathophysiological effects of the hormone are induced when bound to AT1 such as vasoconstriction, increased thirst, aldosterone production, Na+ reabsorption, nervous sympathetic system activation, hypertrophy and fibrosis [4]. AT2 is the predominant fetal isoform, and its expression is low in most tissues. AT2 mediates its actions through protein tyrosine phosphatase activation, nitric oxide generation, and sphingolipid signaling to stimulate vasodilation, natriuresis, anti-inflammatory and anti-fibrotic actions [8,9]. Thus, AT1 and AT2 receptors have opposite functions in several cell types [10]. The explanation of AT1 and AT2 functions in adipocytes will be described in this review.

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Other angiotensin peptides hydrolyzed from AGT also have biological effects. These are angiotensin 2–8 (Ang III), angiotensin 3–8 (Ang IV), and angiotensin-(1–7) [Ang (1–7)]. The peptides Ang III and IV can be generated from Ang II degradation at the N-terminal by aminopeptidase (A and M), whereas Ang (1–7) is formed from Ang II through ACE2 [11]. Ang (1–7) acts via the Mas receptor (MasR), and Ang IV binds to the AT4 receptor, which is associated with insulin-regulated aminopeptidase (IRAP) (Fig. 1).

It is in the endocrine pathway that Ang II is produced in the circulation and exerts its biological function in the vasculature or in distinct tissues. However, the RAS is significantly more complex. To deal with such complexity, the RAS can be divided into the endocrine and local systems. The local RAS is defined by Ang II production from AGT and locally synthesized enzymes [12]. Because AGT is a secretory protein, Ang II could be produced inside the cell or in the interstitial space; consequently, the hormone could be bound to its receptor in neighboring cells, thus acting in an autocrine or paracrine manner [13]. Local Ang II production relies on additional enzymes such as tonin, D and G cathepsin and chymase. For example, chymase converts 90% of Ang I to Ang II in myocardial extracts [14,15]. In addition, cultured skeletal muscle fibers and myoblasts lack renin mRNA, while cathepsin D is expressed during stretching when RAS components are up-regulated [16]. Other tissues that have been described to contain the local RAS are the kidney, pancreas, heart, adipose tissue, muscle, liver, adrenal glands and bone marrow [17–20]. Thus, the local RAS in distinct tissues acts via autocrine and paracrine mechanisms to exacerbate the effects of circulating RAS and/or works independently to induce a response within a tissue or cell type.

2. The local RAS in adipocytes and its metabolic role

Adipose tissue has recently been described as an endocrine organ with a great impact on energy metabolism. Thus, adipocyte homeostasis is required to maintain the equilibrium between nutrient utilization and storage. Adipocyte functions include balanced hormonal secretion, sensing hormones and other signals, performing lipogenesis and lipolysis at equilibrium, and normal adipocyte growth and development. Other general adipocyte functions are metabolic processes such as angiogenesis, extracellular matrix reformation, steroid metabolism, immune responses and hemostasis [21].

Additionally, recent findings demonstrate that human and rodent adipose tissues also contain all of the RAS components. AGT messenger RNA (mRNA) expression has been demonstrated in rat white and brown adipose tissue, although greater gene expression is found in white adipose tissue. Because adipose tissue contains several cell types aside from adipocytes such as preadipocytes, monocytes, macrophages, vascular stromal cells, nerve cells and fibroblasts, it became essential to determine whether adipocytes were responsible for adipose tissue AGT or other RAS component production. Several reports demonstrate that isolated adipocytes from humans [22] and rodents [23] as well as the white adipocyte cell line 3T3-L1 all synthesize AGT [24]. Adipose tissue is a major contributor of extrahepatic AGT, particularly in obesity [25,26], and AGT mRNA expression is higher in human visceral adipose depots than subcutaneous adipose depots [27]. Accordingly, production of AGT in adipose tissue (especially in visceral adipose tissue) in obese individuals increases circulating AGT levels as a precursor that can be

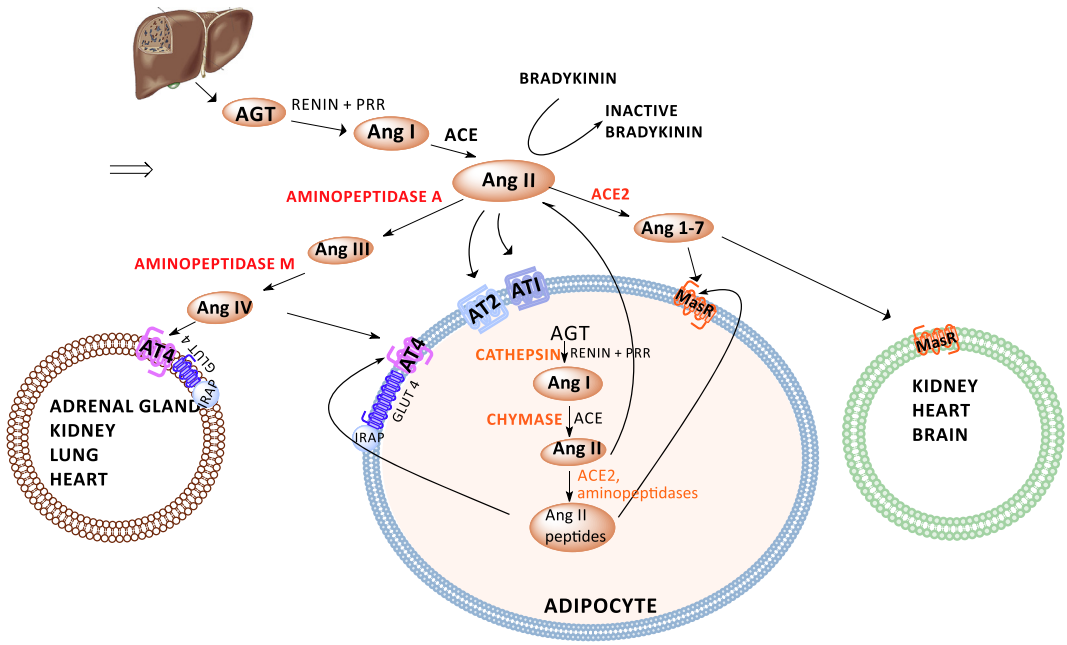

Fig. 1. The RAS. The classical RAS comprises a series of steps that take place in the circulation. The precursor AGT is converted to Ang I through renin, which bound to the PRR is a more potent enzyme. Ang I is cleaved into Ang II by the ACE. This same enzyme inactivates the vasodilator bradykinin. Ang II is typically the effector hormone of the system and regulates blood pressure acting as a vasoconstrictor. The actions of Ang II are mediated by two receptors: AT1 and AT2, which usually have opposing effects. The novel RAS comprises angiotensin peptides derived from Ang II, which include Ang III and Ang IV. These are synthesized by aminopeptidase A and M, respectively. Ang II is also a precursor of Ang(1–7), produced by the action of ACE2. The receptor for Ang IV is AT4, which is bound to IRAP in the plasma membrane, and the receptor for Ang (1–7) is Mas. Apart from renin and ACE found in the bloodstream and tissues, cathepsins and chymase catalyze the production of Ang II locally in various tissues. Note that the classical RAS is represented in black text, the novel RAS in red, and the RAS local enzymes in orange. Angiotensin II and other angiotensin peptides can bind their receptors (AT1, AT2, MasR, and AT4) in several cell types including the adipocyte. PRR: prorenin receptor; AT4: angiotensin receptor type IV.