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Review

The renin angiotensin system, oxidative stress and mitochondrial function in obesity and insulin resistance

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ABSTRACT

Obesity is a complex disease characterized by excessive expansion of adipose tissue and is an important risk factor for chronic diseases such as cardiovascular disorders, hypertension and type 2 diabetes. Moreover, obesity is a major contributor to inflammation and oxidative stress, all of which are key underlying causes for diabetes and insulin resistance. Specifically, adipose tissue secretes bioactives molecules such as inflammatory hormone angiotensin II, generated in the Renin Angiotensin System (RAS) from its precursor angiotensinogen. Accumulated evidence suggests that RAS may serve as a strong link between obesity and insulin resistance. Dysregulation of RAS also occurs in several other tissues including those involved in regulation of glucose and whole body homeostasis as well as insulin sensitivity such as muscle, liver and pancreas and heart. Here we review the scientific evidence for these interactions and potential roles for oxidative stress, inflammation and mitochondrial dysfunction in these target tissues which may mediate effects of RAS in metabolic diseases.
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1. Introduction

Obesity is a major epidemic in the United States and worldwide and is associated with the over-expansion of adipose tissue, insulin resistance, as well as metabolic derangements such as increases in blood pressure (hypertension), blood glucose (diabetes) and lipids levels [1]. It is characterized by chronic low-grade systemic inflammation, which in part emanates from adipose tissue inflammation [2]. This occurs when immune cells such as macrophages and T cells infiltrate adipose tissue as obesity develops [3]. Research has documented key roles for M1 macrophages in obesity-related inflammation [2]. These cells secrete pro-inflammatory substances (such as adipocytokines or adipokines) which spill into the bloodstream and contribute to systemic inflammation [4]. The inflammatory adipokines include angiotensin II (Ang II), a well-known hypertensive hormone generated from the Renin Angiotensin System (RAS) which will be the focus of this review as it relates to inflammation, oxidative stress and mitochondrial dysfunction as possible mechanisms linking RAS to obesity and insulin resistance.

RAS is a major physiological system which regulates blood pressure, fluid and electrolyte balance and is implicated in the pathogenesis of obesity, inflammation, oxidative stress and insulin resistance [5]. Indeed, discovery of the presence of a functional local pancreatic and adipose RAS by a few laboratories, including ours, was unexpected. Moreover, oxidative stress leading to mitochondrial dysfunction has been described in various systems including heart, liver, kidney,

Abbreviations: 20-HETE, 20-hydroxyeicosatetraenoic acid; ACE, angiotensin converting enzyme; ACEI, angiotensin converting enzyme inhibitor; Agt, angiotensinogen; Agt −/−, Agt whole body knock-out mouse model; AMPK, AMP-activated protein kinase; Ang II, angiotensin II; ARB, Ang II receptor blocker; AT1R or AGT1R, Ang II type 1 receptor; AT2R or AGT2R, Ang II type 2 receptor; ATM, adipose tissue macrophages; db/db, obese diabetic mouse model; ERK1, extracellular signal-regulated kinases; GLUT4, glucose transporter 4; HFD, high fat diet; IL, interleukin; IR, insulin Resistance; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinases; KKAY, genetically obese diabetic mouse model; M1, classically-activated macrophages; M2, alternatively-activated macrophages; NADPH, nicotinamide adenine dinucleotide phosphate; NAFLD, non-alcoholic fatty liver disease; NF-κB, nuclear factor-κB; NO, nitric oxide; NOX, NADPH Oxidase; L-NAME, N^{w}-nitro-L-arginine methyl ester; Prx-3, peroxiredoxin-3; PGC-1α, PPARγ coactivator 1α; PI3K, Phosphatidylinositol trisphosphate; PKC, protein kinase C; RAS, renin-angiotensin system; ROS, reactive oxygen species; Sirts, sirtuins; TNFα, tumor necrosis factor; T2D, type 2 diabetes; XO, xanthine oxidase.

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muscle, adipose and pancreas with dysregulated RAS expression or activity [6–12].

Although the link between obesity, insulin resistance and metabolic syndrome is well established [13], the mechanisms linking these complex diseases are yet to be determined. In this context, increased oxidative stress and mitochondrial dysfunction are emerging as important mechanistic links between obesity, and metabolic co-morbidities such as insulin resistance (IR) and Type 2 diabetes (T2D) [14]. Indeed, individuals with obesity exhibit high systemic oxidative stress which is reduced following weight loss [15,16]. Similarly, angiotensinogen (Agt) increases proportionally to body mass index, suggesting that Agt levels and oxidative stress may be closely intertwined. Moreover, both systemic and adipose RAS are overexpressed and/or over activated in obesity [5]. More interestingly, systemic RAS is known to increase vascular oxidative stress and considered to be important in the pathogenesis of hypertension [17]. Taken together, these findings suggest that RAS could be a potential link between obesity, oxidative stress, mitochondrial dysfunction and insulin resistance. Here, we review evidence from published research addressing these interactions.

1.1. Components of the RAS

The RAS involves the precursor protein Agt secreted from the liver into the blood where it is cleaved twice, first by renin (produced by the kidneys) and then by angiotensin converting enzyme (ACE, produced in the lungs). This cleavage cascade results in the hormone, Ang II (Fig. 1), which then acts on several other organs (including the hypothalamus, adrenal glands, kidneys and arterioles) to elicit responses described previously [5,18,19]. While Ang II is the main hormone cleaved from Agt, and the major player in RAS, several other peptides including Ang I, Ang (1–9) and Ang (1–7) are also produced during this process. Ang I is then further cleaved either by ACE to produce Ang II (8 amino acids) or by ACE2 to produce Ang (1–9). Lastly, Ang (1–7) is produced either when Ang II is cleaved by ACE2 or when Ang (1–9) is cleaved by ACE [5,18].

The biological effects of Ang II are mediated through two major G-protein coupled receptors, Ang II type 1 (AT1R or AGTR1) or Ang II type 2 (AT2R or AGTR2). AT1R-mediated signaling molecules include G-protein derived second messengers, protein kinases and small G-proteins (Ras, Rho, Rac, etc.) [20], whereas AT2R effects are mediated via protein tyrosine phosphorylation, sphingolipid signaling and nitric oxide (NO) generation [21]. Most of the physiological functions of Ang II are induced when it is bound to AT1R, e.g. vasoconstriction, aldosterone production, nervous sympathetic system activation and Na^+ reabsorption. Ang II binding to AT2R, however, has been shown to induce vasodilation, and Na^+ excretion (Fig. 1) [22].

1.2. Association between RAS, obesity and insulin resistance

It was not until about 15 years ago that it was discovered that most, if not all, of the major components of RAS can be produced locally in various tissues including adipose and pancreas [23–25]. In fact, Ang II is one of the major pro-inflammatory adipokines produced in obese adipose tissue that may be critical in linking obesity, inflammation and IR [5,18,19,26,27]. Adipose Agt contributes to roughly one third of the circulating Agt in rodents and plays an important role in adipose tissue function through the modulation of adipogenesis or lipid metabolism [28]. The role of Agt was interrogated using mouse models where Agt was manipulated systemically. Whole body Agt knockout mice ($Agt^{-/-}$) exhibited not only reduced blood pressure as expected, but also had decreased adipose tissue growth, whereas over expression of Agt in mice leads to increased adiposity and total fat mass independent of fat free mass [29,30]. This was followed by studies using inhibitors of RAS pathway. Ang II receptor blocker (ARB) olmesartan when given to mice, lowers systolic blood pressure, inhibits adipocyte hypertrophy, suppress (interleukin) IL-6 expression and ameliorates oxidative stress

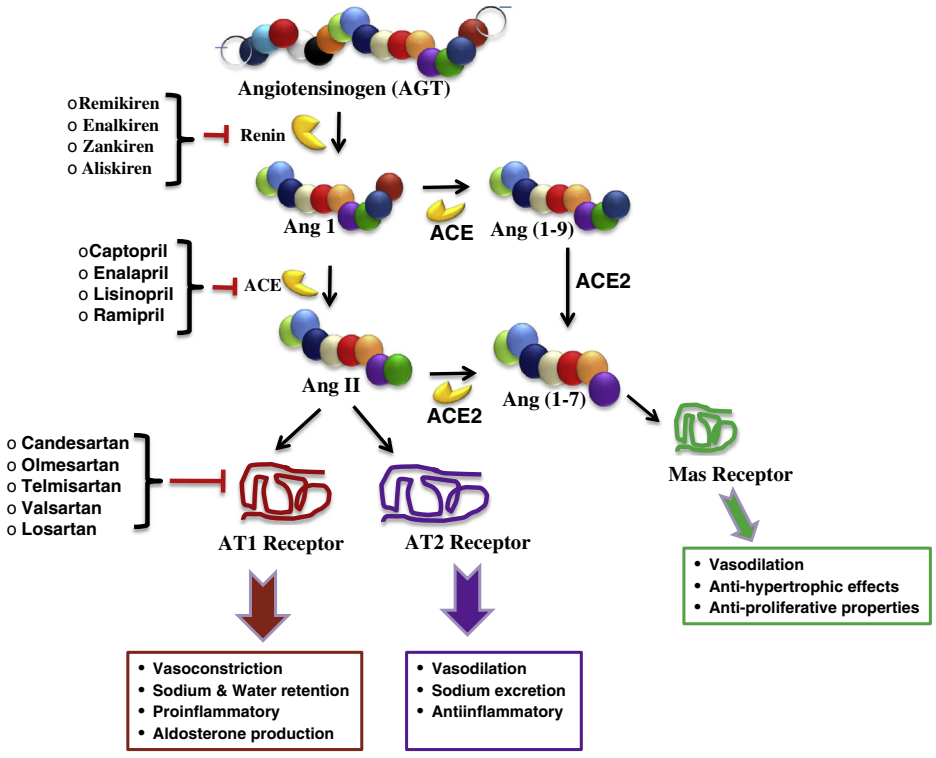

Fig. 1. *Cleavage Cascade for Angiotensinogen.* Schematic depicting the enzymatic cleavage cascade that produces various components of RAS. Receptors for Ang II and Ang (1–7) are also shown along with some of their known functions. Ang = angiotensin, ACE = Angiotensin Converting enzyme.

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