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Angiotensin II and human obesity. A narrative review of the pathogenesis.

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Keywords: obesity; angiotensin II; co-morbidities; adipose tissue; inflammation.

Abstract. Angiotensin II (Ang II) is a hormone and the main effector of the renin-angiotensin system (RAS). This peptide has crucial pathophysiological effects on hypertension, cardiac hypertrophy, endothelial proliferation, inflammation and tissue remodelling through G protein-coupled receptors. The pro-inflammatory role of Ang II has been reported in various inflammatory processes. Obesity is linked to a chronic inflammatory process which in turn is the cause of some of its morbidities. Ang II is related to the comorbidities related to the comorbidities of obesity, which include alterations in the heart, kidney, hypertension and coagulation. In this regard, activation of AT1 receptors by Ang II can induce an inflammatory process mediated by the transcription factor NF-kB, triggering inflammation in various systems that are related to the comorbidities observed in obesity. The aim of this review was to highlight the pro-inflammatory effects of Ang II and the alterations induced by this hormone in various organs and systems in obesity. The search was done since 1990 through Medline, EMBASE and PubMed, using the keywords: *angiotensin II; angiotensin II, obesity; angiotensin II, kidney, obesity; angiotensin II, coagulation, obesity; angiotensin II, inflammation, obesity; angiotensin II, adipose tissue, obesity; angiotensin II, hypertension, obesity; angiotensin II, insulin resistance, obesity; angiotensin II, adiponectin, leptin, obesity; angiotensin II, COVID-19, obesity.* Angiotensin II through its interaction with its AT1 receptor, can induce alterations in diverse systems that are related to the comorbidities observed in obesity. Therapeutic strategies to decrease the production and action of Ang II could improve the clinical conditions in individuals with obesity.

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Angiotensina II y obesidad humana. Revisión narrativa de la patogénesis.

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Palabras clave: obesidad; angiotensina II; co-morbilidades; tejido adipose; inflamación.

Resumen. La angiotensina II (Ang II) es una hormona y el principal efector del sistema renina-angiotensina (SRA). Este péptido tiene importantes efectos fisiopatológicos en la hipertensión, la hipertrofia cardíaca, la proliferación endotelial, la inflamación y la remodelación tisular a través de receptores acoplados a la proteína G. El papel pro-inflamatorio de la Ang II se ha reportado en diversos procesos inflamatorios. La obesidad está ligada a un proceso inflamatorio crónico que a su vez es causa de algunas de sus morbilidades. Se ha demostrado que la Ang II está relacionada con las comorbilidades de la obesidad, que incluyen alteraciones en el corazón, el riñón, la hipertensión y la coagulación. En este sentido, la activación de los receptores AT1 por la Ang II puede inducir un proceso inflamatorio mediado por el factor de transcripción NFkB desencadenado inflamación en diversos sistemas que se relacionan con las co-morbilidades observadas en la obesidad. El propósito de esta revisión fue destacar el efecto pro-inflamatorio de la Ang II y las alteraciones inducidas por esta hormona en diversos órganos y sistemas en la obesidad. La búsqueda se hizo desde 1990 a través de Medline, EMBASE and PubMed, utilizando las palabras clave: *angiotensina II; angiotensina II, obesidad; angiotensina II, riñón, obesidad; angiotensina II, coagulación, obesidad; angiotensina II, inflamación, obesidad; angiotensin II, adipose tissue, obesidad; angiotensin II, hipertensión, obesidad; angiotensin II, resistencia a la insulina, obesidad; angiotensin II, adiponectina, leptina, obesidad; angiotensina II, COVID-19, obesidad.* La angiotensina II a través de su interacción con su receptor AT1 puede inducir alteraciones en diversos sistemas que están relacionados con las comorbilidades observadas en la obesidad. Estrategias terapeúticas para disminuir su producción y la acción de la AngII pudieran mejorar las condiciones clínicas en individuos con obesidad.

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INTRODUCTION

Angiotensin II (Ang II) is a hormone derived from the enzymatic digestion of Angiotensin I by the ACE-1 enzyme in the renin-angiotensin system (RAS). In addition to its vasopressor property, this hormone interacts with its AT1 receptor inducing proinflammatory effects through the NF-kB transcription factor and producing gene activation that transcribes proinflammatory proteins and molecules involved in oxidative stress, among others [1-6]. In this way, Ang II induces several inflammatory processes. It has been reported that obesity is highly involved in chronic inflammation [7-9] and that Ang II may play an important role in that inflammation [1, 10-14]. Obesity constitutes a public health problem in view of the associated comorbidities. The comorbidities associated with obesity reach practically all organ systems: type 2 diabetes mellitus, glucose intolerance,

dyslipidemia, hypertension, coronary and peripheral arteriosclerosis and venous insufficiency are some of them. Many of these comorbidities are associated with the inflammatory process of obesity [15]. At the time of the pandemic induced by SARS-CoV-2 (COVID-19), obesity, being an inflammatory process accompanied by several comorbidities, represents a high risk factor for progression to severe disease and death [16]. During COVID-19 there is an increased pro-inflammatory process mediated by Ang II involving high production of cytokines (cytokine storm) [17]. This inflammatory process in a patient with obesity and comorbidities could further exacerbate the already existing inflammation in these patients and determine a severe evolution. In this regard, Ang II has been implicated in the inflammatory process of obesity and its comorbidities [1-6] . Previous studies have shown an increase of serum pro-inflammatory proteins and high expression of AT1 receptor on circulating leukocytes during the onset of the inflammatory process in obesity without co-morbidities [8]. This suggests an initial susceptibility to the action of Ang II in the obesity inflammatory process. Therefore, this review aims to describe the proinflammatory mechanism of Ang II and the possible mechanisms by which Ang II is involved in obesity.

Angiotensin II overview

Angiotensin II is an octapeptide that belongs to the renin–angiotensin system (RAS) and is produced by cleavages of renin forming Ang I that in turn is converted to Ang II by angiotensin converting enzyme-1 (ACE 1). This conversion to Ang II involves the RAS pathway (angiotensin-converting enzyme: ACE); however, the non- RAS pathway (Cathepsin D, Cathepsin G) can also participate in Ang II production. The angiotensinogen is produced in the liver, while renin is produced in the kidney and Ang II in the vascular tissue [2]. ACE2 is another carboxypeptidase that cleaves one amino acid from Ang II leading to the production of the heptapeptide vasodilatory Ang 1–7 [3, 4] and the balance between ACE1 and ACE2 is crucial for controlling Ang II levels [18] . Levels of Ang II can also be regulated by chymase expressed in several tissues (chymase-dependent Ang II-generating system) [19]. These enzymes represent an alternative pathway to ACE in cardiac, vascular, and renal tissue [19, 20]. Other aminopeptidases can cleave Ang II and generate Ang III (2–8) and Ang IV (3–8). Angiotensin III has similar effects to Ang II, although with lower potency (Fig. 1) [5, 21]. Angiotensin IV exerts a protective role by increasing blood flow in the kidney [22] and brain[23]. The presence of RAS components has been observed locally in several organs including the heart [24], kidney [25], brain [26], pancreas [27], and adipose tissues [28], where they have different functions and can operate independently. In addition, a functional intracellular RAS has been identified [29, 30]. The presence of local and intracellular RAS suggests autocrine and apocrine effects of Ang II in different tissues including proinflammatory, proliferative, and pro-fibrotic activities. In this regard, Ang II induces oxidative stress, apoptosis, cell growth, cell migration and differentiation, extracellular matrix remodeling, regulation of inflammatory gene expression and can activate multiple intracellular signaling pathways leading to tissue injury [14, 31]. According to this, the mechanisms of Ang II action can be autocrine, paracrine, and endocrine.

Angiotensin II acts through two distinct G protein-coupled receptors, angiotensin type 1 (AT1, isoforms A and B) and the type 2 (AT2) receptors [6, 32]. AT1A confers actions of Ang II such as blood pressure increase [33], salt retention in proximal tubular cells [34], aldosterone release [35], and stimulation of the sympathetic nervous system in the brain [36]. AT1B regulates blood pressure when AT1A receptor is absent [37]. AT1 and AT2 receptors have counter-regulatory actions in the cardiovascular and renal system [38]. AT2 receptor induces vasodilation and improves artery remodeling and it is upregulated during cardiovascular injury [37]. Angiotensin II

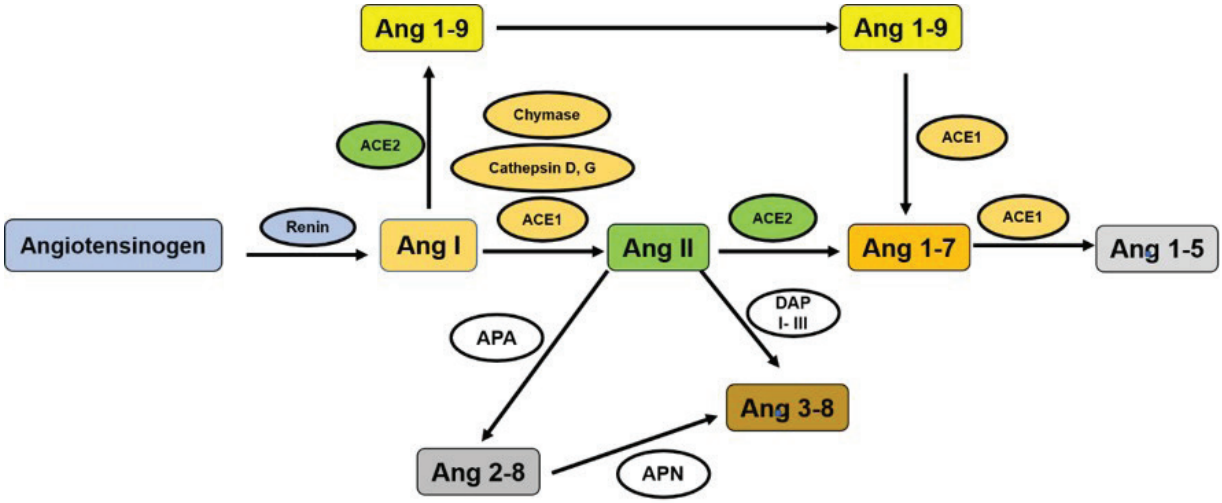

Fig. 1. Renin angiotensin system. The angiotensinogen is transformed into Ang I by the action of the enzyme renin. Ang I is transformed into Ang II by the action of ACE 1, cathepsins D and G or by chymase. In addition to, Ang I can be converted into Ang 1-9 by ACE2 that under the action of ACE 1 converted into Ang 1-7. Ang II can also be converted into Ang 1-7 by ACE2 which under the action of ACE 1 can be transformed into Ang 1-5. Various aminopeptidases can act on Ang II to produce Ang 2-8 and Ang 3-8. ACE 1: angiotensin converting enzyme-1; ACE 2: angiotensin converting enzyme-2; DAP I-III: Dipeptidyl-aminopeptidase I-III; APA: aminopeptidase A; APN: aminopeptidase N; Ang I: angiotensin-I; Ang II: angiotensin-II; Ang 1-5: angiotensin-1-5; Ang 1-7: angiotensin-1-7; Ang 1-9: angiotensin-1-9; Ang 2-8: angiotensin-2-8; Ang 3-8: angiotensin-3-8.

also activates AT1 receptor to induce pro-inflammatory, vasoconstriction, and fibrosis effects; however, activation of AT2 receptor to induce pro-inflammatory effect through NF-kB pathway activation has been also reported [38-40]. AT1 and AT2 receptors also bind Ang III (2-8) and AT4 receptor binds Ang IV (3-8) [41].

Obesity and Inflammation

Obesity is associated with chronic inflammation that increases the risk of developing metabolic diseases, which include hypertension, insulin resistance (IR), altered glucose tolerance, hyperinsulinemia, and dyslipidemia [42]; alterations that together represent the metabolic syndrome (MS). Insulin resistance is a complication of chronic inflammation associated to monocyte/macrophage infiltration and activation of the adipose tissue. This chronic inflammation involves both innate and adaptive immune system [7-10, 43-46] Angiotensin II (Ang II) has been associated to obesity morbidities [10, 47]. During obesity, the precursor of Ang II (angiotensinogen, produced in liver and adipose tissue) is up regulated and related to the growth of adipose tissue and the regulation of blood pressure [11]. Thus, Ang II initiates the activation of an inflammatory process that includes increased oxidative stress, and production of cytokines, chemokines, and growth factors mediated by transcription factor NF-κB activation [1]. In this way, Ang II initiates a chain of inflammatory processes that induce various co-morbidities observed in obesity.

Angiotensin II and adipose tissue

The renin angiotensin system plays a critical role in the pathogenesis of obesity, obesity-associated hypertension, and IR [10]. Angiotensin II can be produced by human adipose tissue; in this regard, angiotensinogen and the enzymes involved in its conversion to Ang II, and both the RAS (renin,

angiotensin-converting enzyme: ACE) and non- RAS (cathepsin D, cathepsin G) pathways are expressed in human adipose tissue. In addition, Ang II receptors are also expressed in adipose tissue suggesting a local role of this hormone in the regulation of adipogenesis, lipid metabolism and in the pathogenesis of obesity [28, 48]. The influence of Ang II on adipocytes is mediated by AT1 and AT2 receptor activation, involving different systems of signal transduction, including Ca 2+ responses, cell proliferation and differentiation, accumulation of triglyceride, adipokine gene expressions and adipokine secretion [49]. Angiotensin II also has anti-adipogenic effect by reducing differentiation of human pre-adipose cells [50]. Therefore, this hormone could be a protective factor against uncontrolled expansion of adipose tissue [51]. This Ang II anti-adipogenic effect has also been observed in omental fat of humans with obesity, involving the participation of the extracellular signal-regulated kinase/1,2 (ERK/1,2) pathway and the phosphorylation of peroxisome proliferator-activated receptor gamma (pPARG) [52, 53]. During this process, the origin of Ang II can be either by RAS or by non-RAS pathways, the latter may be more important in this process [54] . However, in addition to this effect, Ang II can increase triglyceride content and the activities of two lipogenic enzymes (FAS: fatty acid synthase, and GPDH: glycerol-3-phosphate dehydrogenase) in primary cultures of human adipose cells, suggesting control of adiposity through regulation of lipid synthesis and storage in adipocytes [55]. Ang II also regulates the regional blood flow to adipose tissue and the size and number of fat cells [56]. These findings have been confirmed by experimental blocking of Ang II, which directly influences body weight and adiposity (Fig. 2) [57].

The autocrine regulation of Ang II during adipogenesis has also been documented. Angiotensin II can be catabolized in adipose tissues by adipose angiotensin-converting enzyme 2 (ACE2) to form Ang 1-7. The autocrine regulation of the local angiotensin system implies co-expression of Ang II receptors (AT1 and AT2) and Ang 1-7 receptors (Mas) on adipocytes. Activation of the Mas receptor by Ang 1-7 has an effect contrary to the anti-adipogenic effect of Ang II by inducing adipogenesis via activation of PI3K/Akt and inhibition of MAPK kinase/ERK pathways [58]. In this context, the autocrine regulation of the Ang II/AT1-ACE2-Ang 1-7/Mas axis during adipogenesis is capable of producing hormones and cytokines that promote inflammation, lipid accumulation, IR and the components of the RAS, which are activated in the presence of obesity as key obesity-related mechanisms of hypertension and other components of the cardiometabolic syndrome (Fig. 2) [59].

Angiotensin II as a pro-inflammatory agent in obesity

Previous studies have demonstrated the role of Ang II in the inflammation during the obesity. Recently, several experimental studies have shown that Ang II mediates important events of the inflammatory processes [60]. Local activation of RAS and Ang II synthesis increase vascular permeability, mediated by the expression and secretion of vascular endothelial growth factor (VEGF) [61-63], and induce endothelial adhesion molecules expression, such as P and L selectins, vascular cell adhesion molecules-1 (VCAM-1), intercellular adhesion molecules-1 (ICAM-1) and their ligands [64-66], favoring the recruitment of infiltrating inflammatory cells into tissues. In addition, this effect is enhanced by the production of specific cytokine/ chemokines, also mediated by Ang II/ AT1 receptor activation [67-69]. Angiotensin II also promotes endothelial dysfunction through the cyclooxygenase 2 (COX-2) activation, which generates vasoactive prostaglandins and reactive oxygen species (ROS) promoting mitochondrial dysfunction [70-72]. In addition to those effects, a pro-fibrotic effect of Ang II mediated by elaboration of TGF-beta 1, a fibrogenic cytokine responsi-

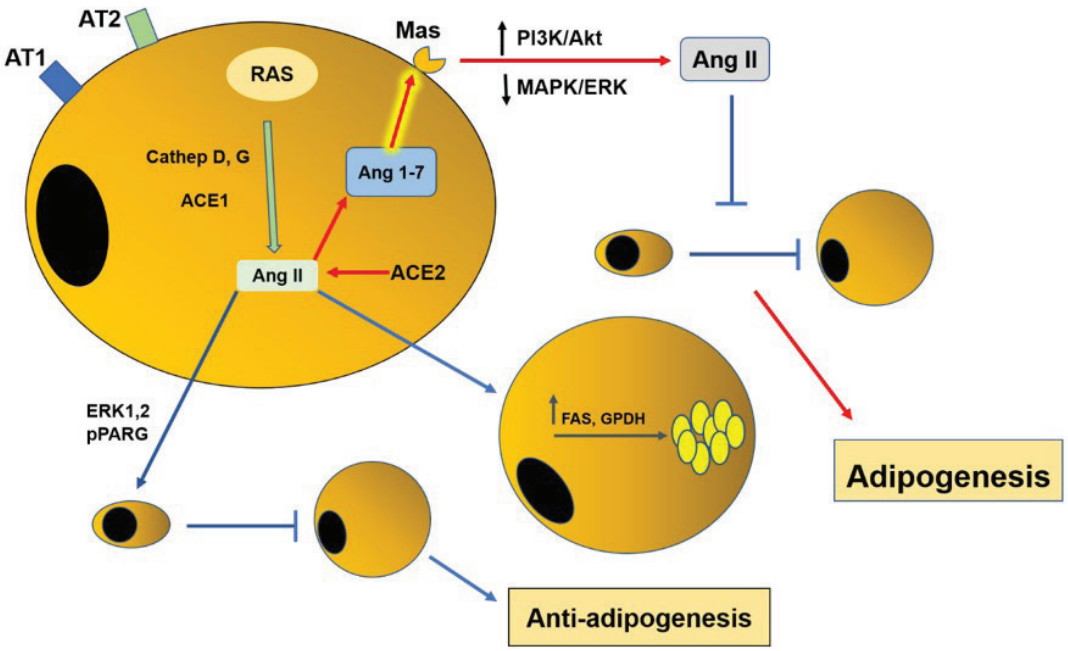

Fig. 2. Adipogenic and anti-adipogenic effects of renin angiotensin system (RAS). Local production of Angiotensin II (Ang II) in adipose tissue, is involved in the regulation of adipogenesis and lipid metabolism. Ang II has anti-adipogenic effect by reducing adipogenic differentiation of human pre-adipose cells involving the participation of ERK(1,2) and the pPARG. Ang II can also increase triglyceride content in adipocytes by activating two lipogenic enzymes, FAS and GPDH. This anti-adipogenic effect of Ang II can be regulated. Ang II can be catabolized by adipose ACE2 to form Ang 1-7 which interacts with Ang 1-7 receptors (Mas) on adipocytes, by activation of PI3K/Akt and inhibition of MAPK kinase/ERK pathways and inducing inhibitory effect in the anti-adipogenic Ang II/AT1, promoting adipogenesis. AT1: Angiotensin II receptor-1; AT2: Angiotensin II receptor-2; RAS: Renin Angiotensin System; Cathep D, G: Cathepsin D, Cathepsin G; ACE1: angiotensin-converting enzyme-1; ACE2: angiotensin-converting enzyme-2; Ang 1-7: Angiotensin 1-7; ERK(1,2): extracellular signal-regulated kinase(1,2); pPARG: phosphorylated peroxisome proliferator-activated receptor gamma; FAS: fatty acid synthase; GPDH: glycerol-3-phosphate dehydrogenase; MAPK kinase/ERK: mitogen-activated protein kinases / extracellular signal-regulated kinases; PI3K/Akt: phosphatidylinositol 3-kinase / protein kinase B.

ble for connective tissue formation and tissular deterioration has been reported [73, 74]. Therefore, Ang II promotes inflammation and tissue injury.

As above explained, Ang II has an important role in the accumulation of body fat during obesity, and obesity is associated with several medical conditions leading to death [75]. In this regard, obesity is associated with the development of hypertension, type 2 diabetes, dyslipidemia, and cardiovascular and renal diseases. Therefore, dysfunction of adipose tissue has been proposed as the cause of visceral obesity-related metabolic disorders, leading to proinflammatory status [76]. In that way, Ang II has been proposed as a promoter of inflammation in obesity associated comorbidities (Fig. 3). Thus, both obesity and hypertension have independently been associated with increased levels of inflammatory cytokines and immune cells within specific tissues, mediated by increased activity of the RAS [12]. Experimental studies have shown association of obesity, Ang II and proinflammatory processes. In this context, consumption of a high-fat diet by mice induces proinflam-

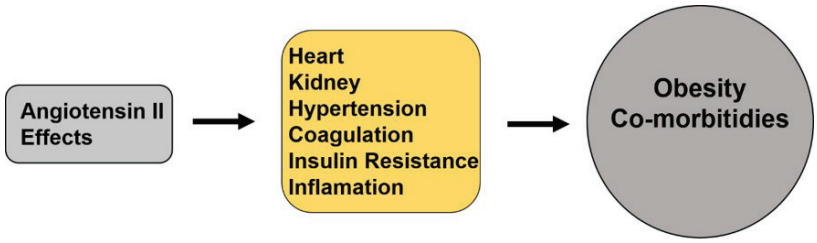

Fig. 3. Pro-inflammatory effects of Angiotensin II (Ang II) on obesity. Ang II is intimately linked to obesity and its pro-inflammatory effects are involved in their co-morbidities, such as insulin resistance, hyperinsulinemia, impaired glucose tolerance, dyslipidemia, and hypertension.

matory responses in the hypothalamus and the subfornical organ, which are known to regulate blood pressure and energy balance accompanied by increased RAS activity [12]. The sensitization of Ang II-elicited hypertension by a high-fat diet in rats was reported, mediated by upregulation of the brain RAS and central proinflammatory cytokines [77]. Exogenous administration of Ang II to rats led to increased monocyte chemoattractant protein-1 (MCP-1) expression in epididymal, subcutaneous and mesenteric adipose tissue. In vitro studies in Ang II treated adipocytes showed increased MCP-1 production mediated by AT1 receptor and NF-kB-dependent pathway, suggesting a link between obesity, Ang II and inflammation [78]. Angiotensin II increases inflammation and endoplasmic reticulum stress in adipocytes via AT1 receptor and mediated by the miR-30 family, -708-5p and/or -143-3p [79]. In a rat model of obesity hypertension, induced by a high-fructose diet, downregulation of adipose RAS, reduced inflammation in adipose tissue and improved obesity hypertension [80].

The initial factors involved in generating the inflammatory events in human obesity remain unclear. Analysis regarding to the presence of Ang II and its AT1 receptor on individuals with obesity, without co-morbidities, showed similar serum levels of Ang II and decreased production of Ang II by circulating mononuclear cells (CMC) in both, individuals with obesity and controls. However, an increased number of CMC expressing the AT1 receptor was observed in individuals with obesity; suggesting that Ang II production does not play an important role in the early period of obesity inflammatory alterations. However, high expression of Ang II receptors may be a preliminary step, with further cellular activation by Ang II [8]. These findings may represent different functional periods of Ang II in the obesity inflammatory events to induce co-morbidities, in which, the initial Ang II pro- inflammatory effects are not found, but in advanced stages of the obesity complications, this molecule may have deleterious effects [8]. In this regard, blocking of Ang II in overweight and patients with obesity associated with multiple comorbidities results in a substantial increase in adiponectin levels and improved IR [13]. Fig. 4 shows in a general way the inflammatory, vasopressor and insulin resistance effects of Ang II.

Angiotensin II and kidney in obesity

Angiotensin II has been implicated in renal damage during obesity. Obesity as a proinflammatory state is associated to kidney diseases and to the development and progression of chronic kidney disease (CKD). Angiotensin II plays an important role in renal damage during obesity. In this regard, increased Ang II contributes to hyperfiltration glomerulomegaly, by altering renal hemodynamics, and subsequent focal glomerulosclerosis [14, 31]. In addition, the imbalance between increased Ang II and the ACE2/Ang 1-7/Mas receptor axis, contributes additionally to renal injury in obesity.

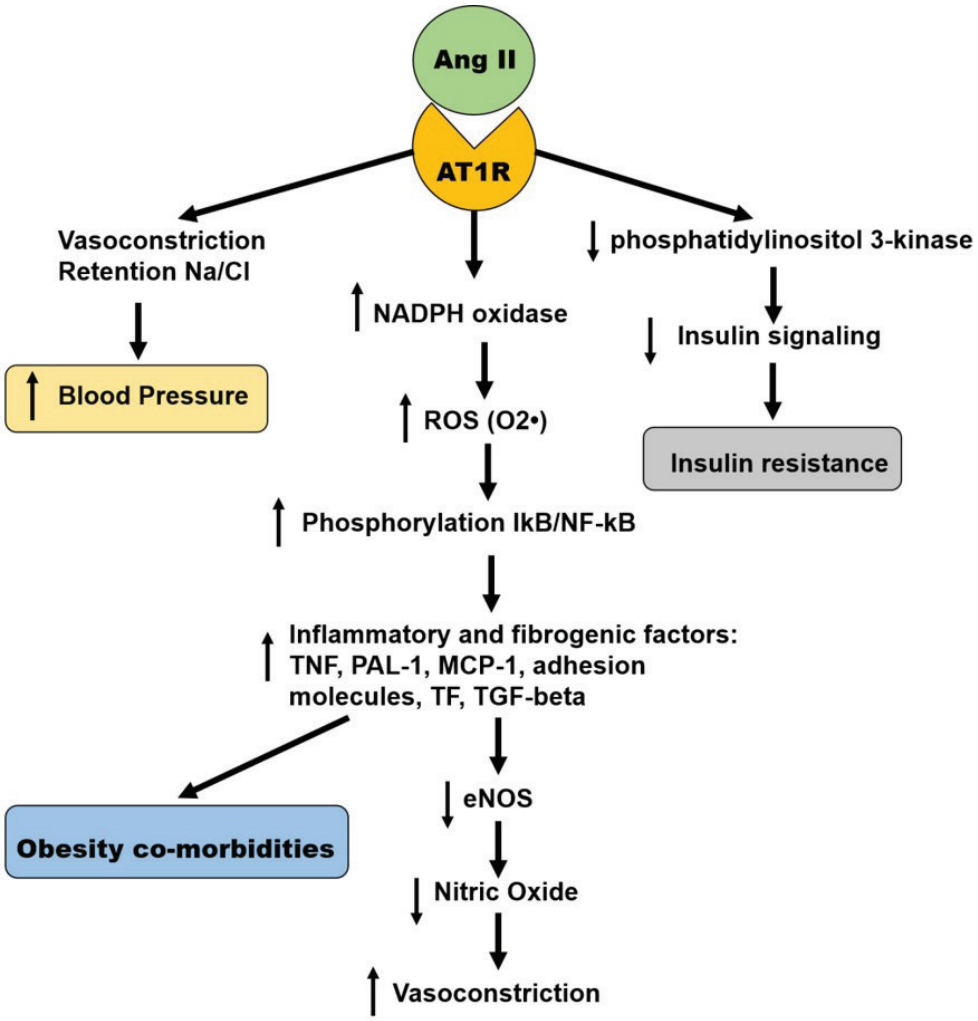

Fig. 4 Interaction of Angiotensin II (Ang II) and its receptor (AT1R) during obesity. After activation of the AT1receptor by Ang II, a series of intracellular processes are initiated that lead to increased blood pressure, insulin resistance and production of co-morbidities during obesity. ROS: reactive oxygen species; TNF: tumor necrosis factor; TF: tissue factor; Pal-1: plasminogen activator inhibitor-1; MCP-1: monocyte chemoattractant protein1; TGF-beta: transforming growth factor-beta; NADPH: reduced form of nicotinamide-adenine dinucleotide phosphate; IkB: inhibitor kB; NFkB: nuclear factor kB; eNOS: endothelial nitric oxide synthase.

The therapeutic blocking of the production or action of Ang II improves the adverse effects on the kidney during obesity [14]. Angiotensin II regulates sodium/fluid homeostasis and blood pressure in the kidney mediated by the activation of AT1 receptors. In obesity, an exaggerated action of Ang II has been implicated in the increased renal sodium retention and the resetting of the pressure natriuresis leading to hypertension. These effects could be related to increased plasma insulin levels observed in obesity which upregulate both AT1 and AT2 receptors in the kidney [81]. During obesity and azotemia, the oxidative stress stimulates synthesis of Ang II, which in turn increases tumor growth factor-beta (TGF-β) and plasminogen activator inhibitor-1 expressions, inducing glomerular fibrosis. Furthermore, in these patients, local synthesis of angiotensinogen by

adipocytes, leptin activation of sympathetic nervous system, and hyperinsulinemia contribute to the development of hypertension and CKD in obesity [82]. Renal abnormalities induced by Ang II in the obesity may also be related to the effects of oxidative stress on the large conductance, Ca (2+)-activated K (+) channels in podocytes. In addition, Ang II induces podocyte apoptosis [83]. Other possible cause of renal failure is the excessive leptin production in patients with obesity. Leptin induces dysfunction of intrarenal vessel endothelium and microalbuminuria and increases circulating endothelin-1. These disorders in obesity can be improved by administration of Ang II receptor blockers [84]. Experimental results show that obesity augments vasoconstrictor reactivity to Ang II in the renal circulation of the Zucker rat, providing insight into early changes in renal function that predispose to nephropathy in later stages of the disease [85]. Considering the data exposed, Ang II has a relevant role in the renal damage during obesity mediated by structural, hemodynamic, and biochemical alterations (Fig. 5).

Angiotensin II and heart in obesity

Previous studies have reported that during obesity, Ang II is able to induce cardiac and arterial damage. Visceral adipose tissue plays a key role in the metabolic and cardiovascular complications in obesity. Angiotensin II may be involved in modulating both intracardiac lipid content and lipid metabolism-related gene expression, in part via AT1 receptor-dependent and pressor-independent mechanism [86]. Angiotensin II and catecholamines may induce increased G protein-coupled receptor kinase 2 (GRK2) lev-

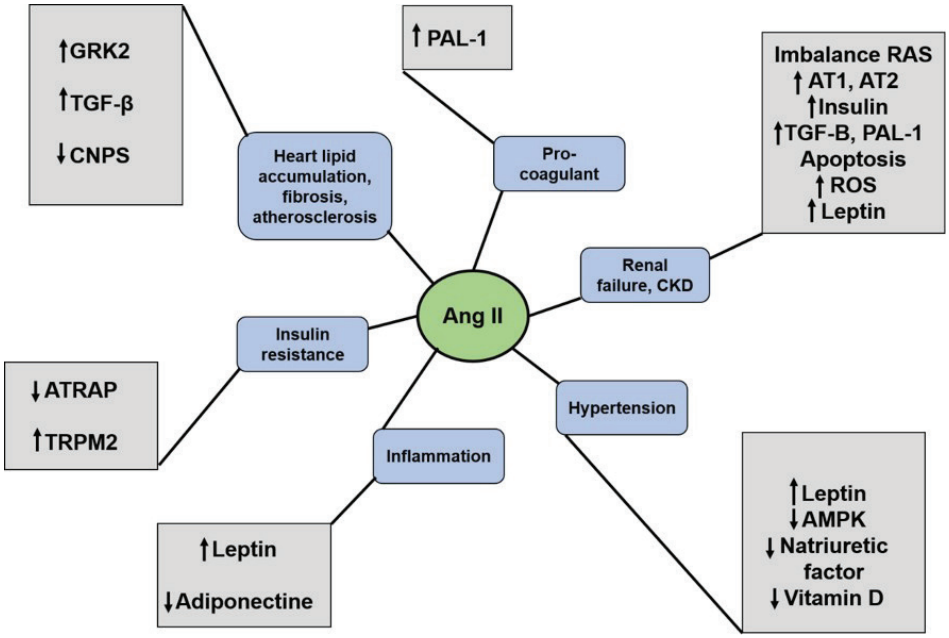

Fig. 5 Effects of Ang II on various organs and systems in obesity. Angiotensin II is involved in various effects on the heart, kidney, insulin resistance, hypertension, coagulation, controlling leptin and adiponectin levels, and inflammatory processes among others during obesity. Ang II: Angiotensin II; AT1: Angiotensin II receptor-1; AT2: Angiotensin II receptor-2; RAS: Renin Angiotensin System; TGF-B: Transforming growth factor-beta; ROS: Reactive oxygen species; AMPK: Adenine monophosphate -activated protein kinase; PAL-1: plasminogen activator inhibitor-1; CKD: Chronic kidney disease; GRK2: G protein-coupled receptor kinase 2; CNPS: cardiac natriuretic peptide system; ATRAP: AT1 receptor-associated protein; TRPM2: Transient receptor potential melastatin 2.

els in diverse cardiovascular cell types. This can explain the contribution of increased GRK2 levels to altered cardiovascular function and remodeling in obesity [87]. Lipid accumulation in the heart is associated with obesity and may play an important role in the pathogenesis of heart failure. Myocyte steatosis can increase the fibrotic effects of Ang II mediated by the activation of TGF-β signaling and increased production of ROS [88]. The visceral adiposity and cardiometabolic complications are linked to IR, sympathetic nervous system, RAS and cardiac natriuretic peptide system (CNPS). Renin angiotensin system and CNPS are antagonistic systems on sodium balance, cardiovascular system, and metabolism. As expressed, RAS activity is increased in patients with obesity; however, CNPS, which induces natriuresis and diuresis, reducing blood pressure, and has powerful lipolytic activity is found reduced in these patients. Thus, reduced CNPS effects coupled with increased RAS activity have a central role in increased obesity cardiovascular risk [89]. During obesity increased serum Ang II and TNF-α levels have also been reported. Experimental data have shown that these two peptides may interact to exacerbate myocardial ischemic/reperfusion injury [90]. Atherosclerosis is a complex, chronic disease that usually arises from the converging action of several pathogenic processes, including obesity, hypertension, hyperlipidemia, and IR. The capacity of Ang II to induce atherosclerosis and cardiovascular injury has been reported in both human and animal studies [91]. Despite the harmful Ang II effects on the heart, some of its metabolites (Ang 1-7) may have beneficial cardiovascular and metabolic effects when Ang 1-7 interacts with the Mas receptor (Fig. 5) [92].

Angiotensin II and hypertension in obesity

Angiotensin II associated with obesity represents a high risk factor of hypertension in obese individuals. Angiotensin II is associated with obesity hypertension [47]. Arterial hypertension represents one of the comorbidities observed in obesity and the renin-angiotensin-aldosterone system is an important effector [93]. Obesity can increase the risk of hypertension and cardiovascular disease in individuals born prematurely, since obesity may increase the prematurity-associated imbalance in the RAS [94]. During obesity increased levels of circulating leptin which can increase sympathetic nerve activity and raise blood pressure have been reported. This leptin induced hypertension is mediated by up-regulation of central RAS and proinflammatory cytokines [95].

Angiotensin II is also capable of suppressing AMPK activity in the kidney, leading to sodium retention, enhanced salt-sensitivity, and hypertension [96]. In addition, obese hypertensive men have a relative natriuretic peptide deficiency and inadequate RAS suppression, one of the mechanisms by which obesity leads to hypertension [97]. Obesity and vitamin D deficiency have both been linked to augmented activity of the tissue RAS. In obesity, decreased levels of 25-hydroxyvitamin D are associated with increased vascular sensitivity to Ang II leading to hypertension (Fig. 5) [98].

Angiotensin II and insulin resistance in obesity

One of the obesity morbidities is the loss of insulin sensitization of the insulin receptor. Previous studies have demonstrated the relationship of Ang II with insulin resistance. Insulin is a hormone that allows glucose to enter cells in different tissues which also reduces blood glucose. Insulin resistance is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase cellular glucose uptake and utilization in consequence blood glucose levels increase. Obesity, sedentarism, and family history of diabetes are some of risk factors for IR [99]. Previous studies have shown that Ang II is an important promoter of IR and diabetes mellitus type 2 [100]. Angiotensin II-induced IR is suppressed by increased AT1 receptor-associated protein (ATRAP) in

adipose tissue, hyperactivity of AT1 receptor induced by Ang II decreases ATRAP and could be related to IR [101]. Other mechanism, as the action of redox-sensitive transient receptor potential melastatin 2 (TRPM2), has been proposed. TRPM2 is a positive regulator of Ang II-induced adipocyte IR via Ca^{2+}/CaMKII/JNK-dependent signaling pathway. Inhibition of TRPM2 improves insulin sensitivity induced by Ang II in adipose tissue [102]. Blocking of the AT-1 receptor also improves IR mediated by Ang II and changes induced by adiponectin in patients with diabetes mellitus [103]. These data suggest that Ang II increases the action of TRPM2 with subsequent IR production (Fig. 5).

Angiotensin II and adiponectin, and leptin in obesity

Angiotensin II may modulate the action of leptin and adiponectin in obesity. There is evidence that dysregulation in the production of adipocytokines is involved in the development of obesity-related diseases. Two important adipocytokines, leptin and adiponectin are associated to obesity, IR, increased risk of coronary heart disease and type 2 diabetes mellitus. Decreased levels of the anti-inflammatory adiponectin, while increased levels of proinflammatory cytokine leptin associated with obesity, IR and endothelial dysfunction have been reported [104]. Leptin and adiponectin have opposite effects on inflammation and IR. Leptin upregulates proinflammatory cytokines such as TNF-α and interleukin-6 associated with IR, type 2 diabetes mellitus and cardiovascular diseases in the obesity [104]. Angiotensin II and its metabolites acting on AT1 receptor can stimulate leptin production in human adipocytes. This effect is mediated by an extracellular-signal-regulated kinase 1 and 2-dependent pathway [105] and can increase the pro-inflammatory activity of leptin during obesity. On the other hand, leptin decreases Ang II-induced vascular effect by blocking the vasoconstrictor action of Ang II and inhibits the Ang II-induced increase in intracellular Ca (2+) in vascular smooth muscle cells [106]. Plasma concentrations of adiponectin correlated negatively with a vast majority of risk factors, such as obesity, type 2 diabetes, glucocorticoids, testosterone, and hyperlipidemia, suggesting a protective role of adiponectin. Blocking of RAS increases plasma adiponectin suggesting a role of Ang II in decreased levels of adiponectin. Supporting this, Ang II infusion decreased plasma adiponectin and adiponectin mRNA in adipose tissue. Angiotensin II also interacts with adiponectin in their target cells. In this regard, the misbalance between adiponectin, Ang II, and IR in endothelial cells can determine the endothelial dysfunction in metabolic syndrome and obesity [107-109]. There is evidence indicating that adiponectin has reno-protective effects and protects against the development of albuminuria induced by Ang II in obesity (Fig. 5) [110], suggesting that Ang II-decreased effect on adiponectin may be involved in renal damage.

Angiotensin II and coagulation in obesity

Angiotensin II may alter the fibrinolytic system in obesity. The connection between obesity and hemostasis disorders is well established. The inhibition of fibrinolysis in the obesity, associated to increased plasma inhibitor, plasminogen activator inhibitor-1 (PAI-1) has been documented [111, 112]. PAI-1 is the main inhibitor of the fibrinolytic system and was recently shown to be produced by adipose cells. Obesity is associated with an increased production and release of PAI-1 protein. Angiotensin II and its metabolites promote PAI-1 production and release by human fat cells and may contribute to the impairment of the fibrinolytic system typical for obesity. AT1 receptor blockade reduces basal and abolishes Ang II-stimulated PAI-1 release from human adipocytes (Fig. 5) [111, 112].

CONCLUSION

The renin angiotensin system and especially Ang II are highly involved in the patho-

logical events that occur in obesity. Angiotensin II through its interaction with its AT1 receptor can induce alterations in diverse systems that are related to the comorbidities observed in obesity. Therapeutic strategies to decrease the production and action of Ang II could improve the clinical conditions in individuals with obesity.

Limitations of the review

The reports studied for this review are only based on the concept of obesity referring to individuals with a BMI greater than 30, with or without morbidities.

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The authors have no competing interests to declare that are relevant to the content of this article.

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Author's contributions

JM-S and ER conceived the subject matter and contributed to the design of the work. JM-S, ER, RV and AP contributed to the acquisition, analysis, or interpretation of data for the work. JM-S and ER wrote the original draft. JM-S, ER, RV and AP critically revised the first draft. All authors approved the final version for all aspects of work ensuring integrity and accuracy.

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