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Angiotensin-(1-7), Adipokines and Inflammation

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ABSTRACT

Nowadays the adipose tissue is recognized as one of the most critical endocrine organs releasing many adipokines that regulate metabolism, inflammation and body homeostasis. There are several described adipokines, including the renin-angiotensin system (RAS) components that are especially activated in some diseases with increased production of angiotensin II and several pro-inflammatory hormones. On the other hand, RAS also expresses angiotensin-(1–7), which is now recognized as the main peptide on counteracting Ang II effects. New studies have shown that increased activation of ACE2/Ang-(1–7)/MasR arm can revert and prevent local and systemic dysfunctions improving lipid profile and insulin resistance by modulating insulin actions, and reducing inflammation. In this context, the present review shows the interaction and relevance of Ang-(1–7) effects on regulating adipokines, and as one adipokine itself, modulating body homeostasis, with emphasis on its anti-inflammatory properties, especially in the context of metabolic disorders with focus on obesity and type 2 diabetes mellitus pandemic.

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Abbreviations: ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; AGT, angiotensinogen; AKT, protein kinase B; Ang II, angiotensin II; Ang-(1–7), angiotensin-(1–7); Ang-(1–5), angiotensin-(1–5); ARB, type 1 angiotensin receptor blockers; AS160, TBC1 domain family member 4; AT1R, type 1 Ang II receptor; AT2R, type 2 Ang II receptor; Bcl-2, B-cell lymphoma 2; eCG, gonadotropic hormone; ERK, extracellular signal-regulated kinases; GLUT4, glucose transporter 4; GSK3B, glycogen synthase kinase 3 beta; IRS, insulin receptor substrate; IR, insulin receptor; JNK, Jun N-terminal kinase; LH, luteinizing hormone; MasR, mas receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF-KB, factor nuclear kappa B; NOS, nitric oxide synthase; PKC, protein kinase C; p38, P38 mitogen-activated protein kinase; RAS, renin-angiotensin system; ROS, reactive oxygen species; IL-1β, interleukin-1β; CXCL1, chemokine (C-X-C motif) ligand 1; SIRT1, Sirtuin 1; TLR4, toll-like receptor 4; NF-κβ, factor nuclear kappa β; MCP-1, monocyte chemoattractant protein-1; VCAM-1, vascular cell adhesion molecule 1; ET-1, endothelin 1.

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1. Introduction

The angiotensin-(1–7) (Ang-(1–7)) is an heptapeptide with significant systemic and local effects, produced in the renin-angiotensin system (RAS) hormonal cascade, with pronounced effects counteracting the angiotensin II (Ang II) actions [1], especially considering Ang II overproduction and high signaling present in several diseases, such as hypertension, diabetes, obesity, renal disorders and liver steatosis [2].

The RAS hormonal cascade initiates with the angiotensinogen (AGT) production, which is cleaved by the renin into angiotensin I (Ang I). Sequentially, the angiotensin converting enzyme (ACE) transforms the Ang I into the octapeptide Ang II, which is the most described active end product of the RAS, acting through two isotypes of Ang II receptors (AT1R and AT2R) [3]. High levels of Ang II produce AT1 hyperactivity and several metabolic disorders [4]. On the other hand, the angiotensin converting enzyme homolog 2 (ACE2) reduces Ang II levels by transforming it in Ang-(1–7), which also can be produced from Ang I passing through angiotensin-(1–9) (Ang-(1–9)) by the action of endopeptidases: prolyl-endopeptidase and neutral endopeptidase. The main described Ang-(1–7) effects are associated with Mas receptor activation, and the ACE2/Ang-(1–7)/Mas arm high activation has been effective in improving metabolic and chronic diseases [5]. Additionally, it is worth mentioning that Ang-(1–7) may be alternatively clived into alamandine that acts via its receptor MrgD, exerting similar actions to Ang-(1–7) [6].

The angiotensin II type I receptors modulate most of the Ang II physiological and pathophysiological effects. The Ang II binding to this receptor leads to vasoconstriction, inflammation, oxidative stress, proliferative factors augmentation, cardiovascular effects, nervous system activation, increased sodium absorption, among other effects. The Ang II type 2 receptors on the other hand, although found in several tissues in the fetal period, has its abundance decreased after birth. These receptors activation are mostly linked to beneficial consequences, including vasodilation, anti-proliferation (fibroblasts, endothelial cells and myocytes), cardiac function improvement and decreased sodium absorption in the proximal tubule [7,8].

The renin-angiotensin system activation is an important defense mechanism against hypovolemic hypotension, commonly observed during bleeding or salt privation. Aldosterone when bound to the mineralocorticoid receptor in epithelial cells of the renal collecting duct recruits sodium channels from the cytosol to the surface of the renal epithelial cells, thereby promoting increased sodium reabsorption, tubular potassium excretion and plasma volume expansion [9]. The aldosterone receptors are expressed in several tissues other than renal; which when disturbed lead to vascular impairments. The aldosterone augments the Ang II actions, inducing vascular remodeling and inflammation, as well as the stimulation of mineralocorticoid receptors in the heart, kidneys, and brain. Moreover, the circulating aldosterone induces cardiac fibrosis and increased sympathetic activity [10].

The RAS upregulation in the central nervous system is characterized by an increased renin activity and high aldosterone levels [11]. Moreover, it was also reported in the literature that in patients with visceral obesity, this hormone levels are normalized following weight loss [12]. In contrast, the renin-angiotensin aldosterone system blockage with ACE inhibitors and AT1R blockers is one of the most used approaches in the treatment of hypertension, congestive heart failure and coronary artery disease [13]. Studies suggest that the mineralocorticoids receptors in adipocytes promote the expression of inflammatory adipokines and facilitate the aldosterone pro-adipogenic effect. These receptors inhibition in experimental studies lead to decreased levels of pro-inflammatory factors in the adipose tissue and increased adiponectin expression in the heart and adipose tissue [14]. In summary, the increased amount of visceral adipose tissue induces the production of aldosterone and other hormones, which facilitates the appearance of chronic inflammation in the adipose tissue and consequent adipokines overexpression.

The Mas receptor (MasR) signaling activated by the Ang-(1–7) has several pathways, however, the most described via includes phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/AKT) or forkhead box protein O1 (FOXO1) [15]. Another crucial signaling effect involves the direct activation of insulin receptor and insulin receptor substrate (IRS) [16,17]. Particularly in the adipose tissue, Ang-(1–7)/MasR axis presents essential effects modulating fat storage, glucose uptake and especially adipokines production regulation [5,18,19], which in turn alter local and systemic inflammation [20–22].

Several studies have shown that Ang-(1–7) exerts inhibitory effects on inflammation and cellular growth mechanisms [23,24]. Ang-(1–7) reduces key molecules signaling pathways thought to be relevant for acute and chronic inflammatory associated diseases. Excess or stressed adipose tissue may work as a systemic pump secreting pro-inflammatory adipokines and reducing the anti-inflammatory hormones [25]. In normal physiology the systemic AGT is mostly produced by the liver, however, in some diseases or hormonal disorders (such as obesity), the white adipose tissue assumes a pivotal role on AGT production, abnormally increasing the Ang II locally and also augmenting circulatory levels [26,27].

Here, we review findings related to the ACE2/Ang-(1–7)/Mas axis function with focus on the role on regulating adipokines secretion and modifying processes associated with acute and chronic inflammation. As most of the studies that involve the Ang-(1–7) signaling pathways were performed under an experimental context with animal models, we opted to discuss the human studies and their clinical importance at the end of each topic.

1.1. Adipokines, angiotensin-(1–7) and adipose tissue

The adipose tissue has long being recognized for its role in body energetic demands supply in a prolonged fasting state, calories storage, body temperature control, and organs mechanical protection [28,29]. Recently, the adipose tissue was defined as an important endocrine organ, responsible for the synthesis and secretion of more than 600 bioactive molecules named adipokines [29]. In mammals there are two main types of adipose tissue, the white adipose tissue (WAT) and brown adipose tissue (BAT). These organs develop opposing roles, as while the WAT acts as by storing energy in the form of lipids, the BAT is responsible for the heat generation via energy consumption. Experimental studies with mice demonstrated that the BAT aids in the protection against the development of obesity and metabolic diseases via activation of thermogenesis [30].

The adipokines are involved in the satiety and appetite regulation, energetic metabolism, fat storage, insulin secretion and sensitivity, arterial pressure, endothelial function and homeostasis [31,32]. At the systemic level, the adipokines act in different target organs, such as liver, brain, muscle, heart, vessels, immunological system and others [31,33–36].

The leptin and adiponectin levels might be used to distinguish the WAT and BAT, as the WAT expresses large amounts of these adipokines, while in BAT these molecules are little expressed, especially when the thermogenesis is active [37]. Similar to the WAT, the BAT also produces bioactive molecules called batokines [38,39]. These molecules may have different and/or opposing actions to the WAT adipokines, and act in different targets (e.g., central nervous system) in the control of energy expenditure. Experimental studies showed that several molecules synthetized by the BAT have already been described to exert autocrine, paracrine and endocrine actions, and the main examples are: Triiodothyronine, prostaglandins, angiotensinogen, interleukin-1α, insulin-like growth factor I, Interleukin-6, vascular endothelial growth factor-A, fibroblast growth factor-2, nitric oxide, and fibroblast growth factor-21 [40–47].

Additionally, studies have reported a different type of adipocytes called beige. These adipocytes are brown-like cells (UCP+), but localized in the WAT [48,49]. These cells are originated from the browning process, which is responsible for the dynamic conversion of white

adipocytes into brown-like adipocytes due to the exposure to physiological, pharmacological or hormonal stimuli [50,51]. The white adipocytes browning is generally induced by the exposure to cold and physical exercise [50,52]. However, this process does not completely transform nor transdifferentiate white adipocytes into brown adipocytes; white adipocytes become only a phenotype resembling a brown adipocyte, which is also called a beige adipocyte [53,54]. The WAT browning exerts regulatory effects on the metabolism, such as increased energy expenditure, weight loss, insulin sensitivity and improved glucose tolerance, and although being performed on a rodent model, open perspectives as a potential target in the prevention and treatment of metabolic diseases, such as diabetes and obesity [55].

Among the main adipokines it is possible to highlight the adiponectin (involved in insulin sensitivity regulation, antidiabetogenic, antiatherosclerotic and anti-inflammatory effects), apelin (insulin secretion inhibition), leptin (appetite and satiety control, energy intake, locomotor activity, energy expenditure, fertility, among others), resistin (related to obesity, insulin resistance and inflammation), proinflammatory adipokines (e.g., interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNFα), monocyte chemoattractant protein-1 (MCP-1), among others), and omentin (anti-inflammatory) [29,31,32].

In the adipose tissue, the adipokines modulate adipocyte functions and metabolism, adipogenesis and immune cells recruitment [32,33,56]. With local action we may cite bone morphogenic protein-4 (BMP-4) that regulates adipogenic cell precursors differentiation, bone morphogenic protein-7 (BMP-7) that stimulates the brown adipose tissue, regulates energy intake, and increases energy expenditure. Ghrelin inhibits BMP-4, BMP-7, and vascular endothelial growth factor (VEGF) that stimulate angiogenesis in the adipose tissue [29,31,32].

As well as the adipokines, the RAS was also described as a critical metabolic regulator. Experimental studies with rodents and humans, linked obesity with the ACE/Ang II/AT1 RAS axis activation [57,58]. The adipose tissue expresses all RAS components, and it is involved in the obesity effects and development due to its increased size, AGT and Ang II production [57]. On the other hand, animal studies evidenced that the RAS counterregulatory axis (ACE2/Ang-(1–7)/Mas) is capable of improving the lipid and glucose metabolism via decreased body adiposity, and directly at molecular signaling levels [27,59]. Mas receptor deficiency in mice was associated with a worse metabolic profile, with lower glucose tolerance, dyslipidemia, hypertension, increased leptin expression, decreased glucose uptake by adipocytes and increased adipose tissue size [27]. In the same way, transgenic rats with Ang-(1–7) overexpression presented improved metabolic efficiency, increased glucose tolerance and insulin sensitivity and higher glucose uptake via insulin [60]. It was also observed lipid parameters improvements with decreased triglycerides and cholesterol, as well as decreased abdominal fat mass in studies performed with rats [60,61].

It has been demonstrated that during adipogenesis, the apelin expression is increased in mice cell lines [62,63]. Some other in vitro studies showed that RAS blockage (Ang II/ACE) improves apelin expression and secretion in adipocytes from mice, which leads to reduced ROS and lipid accumulation in the adipocytes differentiation process [63]. AT1R blockage and consequent AT2R increase reduces TNFα expression and increases apelin expression in the mice white adipose tissue [63,64], suggesting an essential AT2R role in the browning regulation. In humans, apelin seems to induce white adipocyte browning, inhibiting AT1 via its interaction with the apelin receptor (APJ receptor) in vitro [65].

It is important to point that the adipokines may have an indirect effect on the RAS via modulation of insulin levels and lipid profile, thus evidencing an indirect relationship among these molecules. Nickenig and colleagues reported that insulin may upregulate AT1 via posttranscriptional mechanisms, thus linking hyperinsulinemia, hypertension and atherosclerosis [66]. The authors argue that the insulin influence on the RAS, more specifically on the AT1 receptor, takes place via tyrosine phosphorylation and MAP kinase–dependent intracellular pathways. Moreover, the lipid profile has also been associated with the RAS modulation (AT1 upregulation and increased AngII synthesis) [67]. The lipids influence on the AT1 expression and Ang II production, in contrast with the aforementioned insulin effects, seem to be via mRNA stabilization, and increased chymase system activity. As we know and will discuss throughout this review, the adipokines have an important influence on the glycemic and lipid profiles, and this influence may thus explain their relationship with the RAS modulation (Fig. 1).

The interaction between proinflammatory adipokines and RAS is also described in the literature. A study performed with adipose tissue samples from malnourished and obese mice and also confirmed in humans showed that the inflammatory state is shared between these two nutritional states and that the renin-angiotensin system modulates both profiles [68]. Interestingly, it has been reported in the literature that a possible strong influencer of the adipocytes expression/secretion profile is the muscle. The muscle is recognized as another important endocrine organ in our organism and expresses several important molecules, collectively called myokines, which counterbalance the adipokines released by the adipose tissue [69–71]. In this sense, the muscle influence might be also modulating the RAS expression in the adipose tissue.

1.2. Adipokines, Ang-(1–7) and inflammation

In the last years, Ang-(1–7) has been studied for its anti-inflammatory properties in several disorders. Considering metabolic diseases, such as obesity and type 2 diabetes, it was evidenced that increased circulating Ang-(1–7) exerts a protective effect against the inflammatory process induced by obesity by decreasing ciclo-oxigenase-2 (COX-2) and IL-1β expression in transgenic rats' abdominal fat [20]. Additionally, it was shown in another study that oral administration of Ang-(1–7) is capable of preventing obesity and liver inflammation via resistin/toll like receptor 4/Nuclear Factor-kappa β (Resistin/TLR4/NF-kβ) pathway blockage in rats [72], and reduces diet-induced hepatic inflammation by decreasing TNF-α and IL-6 expression [72]. Interestingly, another possible mechanism by which Ang-(1–7) exerts its beneficial effects in inflammatory conditions associated to metabolic disorders in mice, is via Sirtuin 1 (SIRT1), a NAD-dependent deacetylase already described to be involved on improving several metabolic diseases [73].

Interestingly, Ang-(1–7) also ameliorates epicardial adipose tissue (EAT) inflammation induced by obesity. ACE2 knockout obese mice showed increased interferon gamma (IFN-γ) expression in EAT, along with predominant CD11c+/F4/80+ Mf macrophage profile, while treatment with Ang-(1–7) reverted this inflammatory profile, mainly by decreasing TNF-α and IL-6 expression [74]. These findings are noticeable considering that epicardial fat is a current study target aiming to understand the association between obesity, metabolic diseases, and atherosclerosis.

In cardiovascular diseases, especially considering vascular inflammation, Ang-(1–7) diminished macrophage infiltration, MCP-1, IL-6, TNF-α, NFKβ, vascular cell adhesion protein 1 (VCAM-1), reactive oxygen species (ROS) levels, apoptosis and increased nitric oxide release, thus reducing atherosclerosis risks [75]. Furthermore, Ang-(1–7) was capable of resolving endothelial cell inflammation in vivo, thus preventing early atherosclerosis via decreased MCP-1, VCAM-1, IL-6 and atherosclerotic plaque inhibition in human cell lines and knockout APOE mice, both in vitro [76].

The Ang-(1–7) anti-inflammatory effects were also confirmed in rat pancreatic acinar cell lines, where this peptide attenuated caerulein (an acute pancreatitis inducer) induced inflammation by downregulating TLR4/NFKβ pathway [77]. In macrophage cell culture, Ang-(1–7) was capable of preventing proto-oncogene tyrosine-protein kinase Src activation, which are proteins necessary to the inflammatory response induced by lipopolysaccharide (LPS) [78].

In humans studies, endothelial cells culture, Ang II induced inflammation was prevented by Ang-(1–7) via reduced lectin-like oxidized

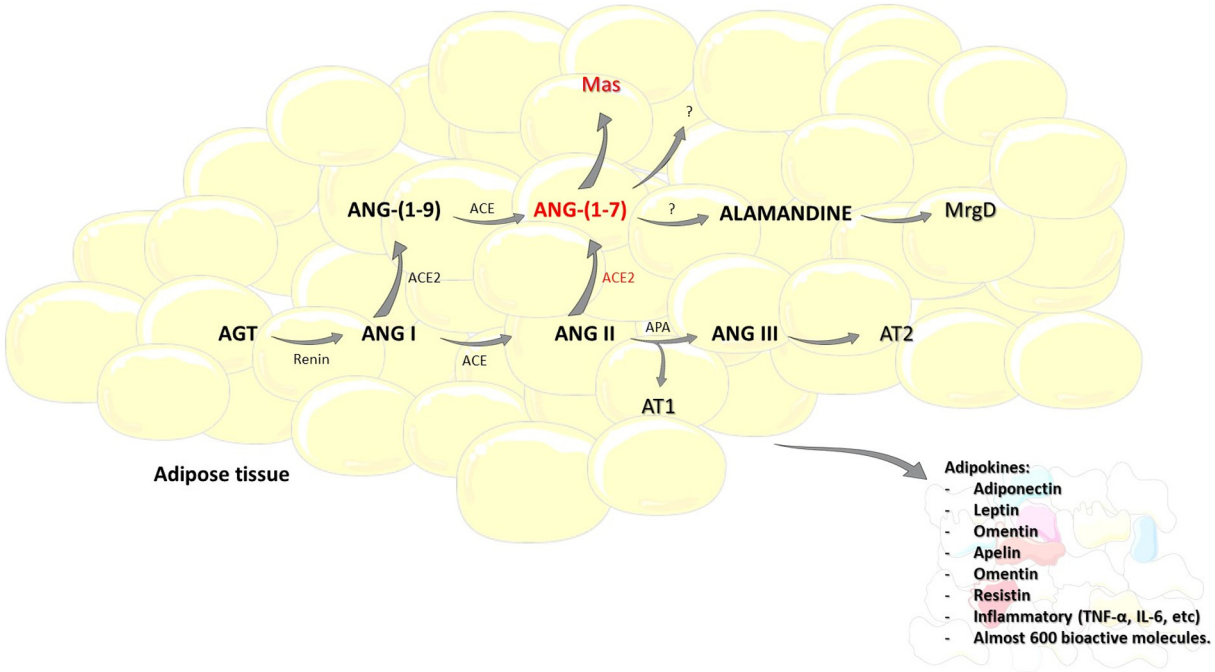

Fig. 1. Renin-angiotensin system and adipose tissue. AGT: angiotensinogen; ANG I: angiotensin I; ANG-(1–9): angiotensin 1–9; ANG-(1–7): angiotensin (1–7); ANG II: angiotensin II; ANG III: angiotensin III; Mas: Mas receptor; AT1: AT1 receptor; AT2: AT2 receptor; ACE: angiotensin-converting enzyme; ACE2: angiotensin-converting enzyme 2; APA: aminopeptidase A; MrgD: Mas-related G-protein coupled receptor D; TNF-α: Tumor necrosis factor alpha; IL-6: Interleukin 6.

low-density lipoprotein (LDL) receptor-1 (LOX-1) expression, a novel scavenger receptor for oxidized LDL (oxLDL), a potent inflammatory activator [79]. In uropathies, which are also characterized by an inflammatory profile, Ang-(1–7) shown to be a protective compensatory molecule reducing inflammatory processes by decreasing macrophage infiltration and apoptosis [80]. The renoprotective role of Ang-(1–7) is mostly discussed and reported by several studies showing neutrophil influx, and downregulation of chemokine (C-X-C motif) ligand 1 (CXCL), IL-6, TNF-α, endothelin 1 (ET-1), IL-1β and MCP-1.

These studies illustrate and confirm the Ang-(1–7) beneficial anti-inflammatory effects in several inflammatory conditions, which are associated with adipokines disruption, such as obesity, type 2 diabetes, cardiovascular diseases, renal and hepatic disorders, among others (Fig. 2).

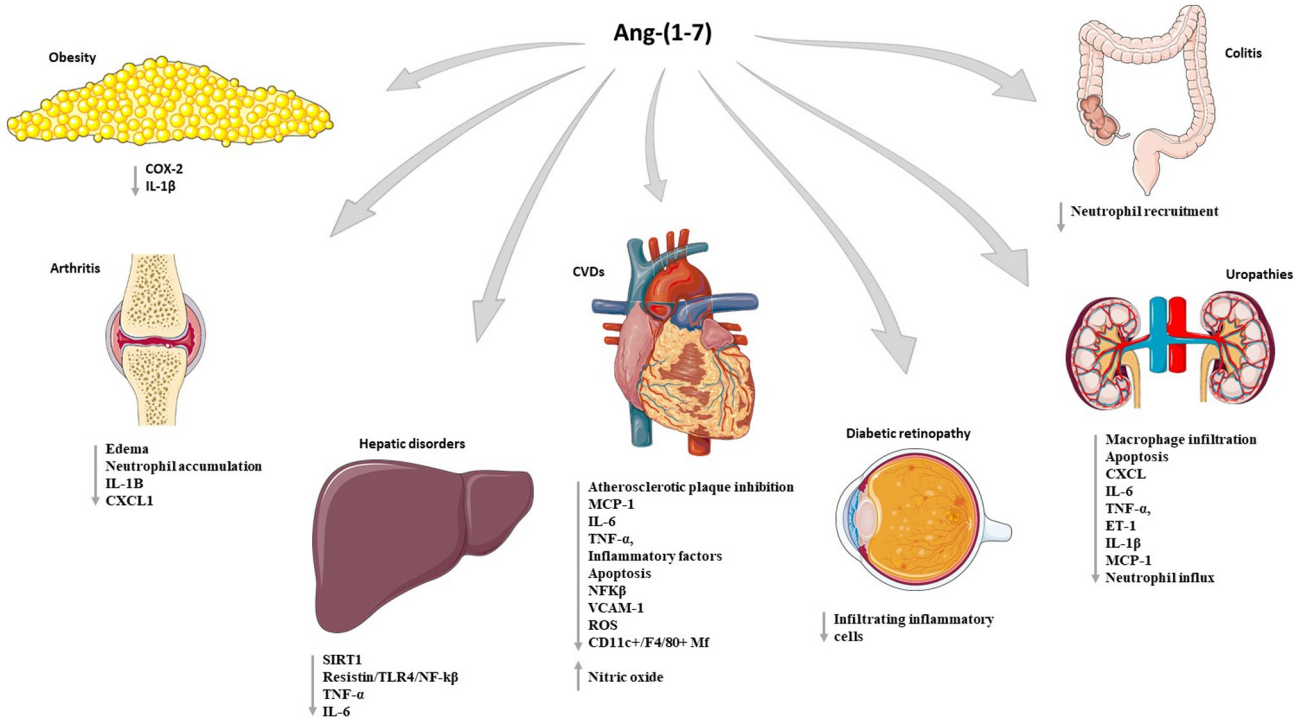

Fig. 2. Ang-(1–7) effects on inflammation. CVDs: cardiovascular diseases; ROS, reactive oxygen species; TNF-α: tumor necrosis factor alpha; IL-6: interleukin 6; IL-1β: interleukin-1β; CXCL1: chemokine (C-X-C motif) ligand 1; SIRT1: Sirtuin 1; TLR4: Toll-like receptor 4; NF-κβ: factor nuclear kappa β; MCP-1: monocyte chemoattractant protein-1; VCAM-1: vascular cell adhesion molecule 1; ET-1: endothelin 1.

1.3. Angiotensin (1–7) and adipokines in different organs

The adipokines produced and released by the adipose tissue mediate the communication network between this tissue and other organs [35]. Modifications in the adipose tissue homeostasis alter the adipokines secretion to a pattern that induces metabolic dysfunctions [33,34]. Angiotensin-(1–7) presents biological and pharmacological properties that are beneficial in the metabolic dysfunctions resolution [81], being relevant to explore the adipokines effects in different metabolic organs, highlighting Ang-(1–7) as a therapeutic tool.

1.3.1. Adiponectin

The adipokines released by the adipose tissue affect several biological processes involved in hepatic function, including angiogenesis, vasodilation, inflammation, and deposition of extracellular matrix proteins, thus modulating hepatic fibrogenesis [82]. In the liver, decreased adiponectin levels may predispose to steatosis and advanced hepatic lesion [82,83]. This adipokine acts by reducing the hepatic stellate cells activation, proliferation, and survivor [76]. Recent studies have evaluated adiponectin analog actions since it is not viable to increase circulating adiponectin levels in humans. These agents attenuate hepatic fibrosis in animal models [84], and have potential to become new anti-fibrotic therapeutic drugs [85].

Taking into consideration the Ang-(1–7) employment for therapeutic purposes, a study from Tang et al. evidenced the Ang-(1–7) therapeutic role in preventing non-alcoholic fatty liver disease (NAFLD) in mice via an adiponectin-independent mechanism, which may be partially attributed to the mitogen activated protein kinases (MAPK) hepatic pathway. The study suggests that Ang-(1–7) treatment may stimulate AMPKα2 expression and 5′ AMP-activated protein kinase (AMPK) phosphorylation, which eventually triggered signaling cascades, being still necessary for further clarification [86]. The RAS positive regulation in hepatic diseases via AT1R/AT2R is directly associated with a pro-fibrotic process, findings evidenced in rat models [87–90]. In a cirrhotic mouse model, increased ACE2 expression inhibited hepatic fibrosis via increased Ang-(1–7), while ACE2 blocking exacerbated the fibrotic process, shedding light to the ACE2 therapeutic potential in the treatment of chronic hepatic lesion [91]. The ACE2/Ang-(1–7)/MasR exerts antifibrotic effects as observed in a hepatic fibrosis animal model where AVE 0991 (Ang-(1–7) agonist) reduced ACE, 1A1 collagen and α-actin expression and hydroxyproline levels, an important collagen component, which all together ameliorates fibrosis [92].

In the mice pancreas, adiponectin stimulates insulin secretion in vivo, and hypoadiponectinemia causes β cells dysfunction [93]. Consistent with these findings, mice without adiponectin exhibited diet-induced hepatic insulin resistance. Adiponectin exerts beneficial effects via activation of its two receptors: adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2) [93,94].

The liver is also an important target in human studies, where hepatic stellate cells isolated from humans cirrhotic liver were shown to overexpress renin, ACE, and Ang II [95]. Increased hepatic stellate cells proliferation and extracellular matrix production via signaling pathways mediated by MAPK, phosphoinositol/Ca2+, and ROS generation are promoted by AT1R/ACE/Ang II axis activation [96–98].

Additionally, the cardiovascular system is another important investigation target in human studies. It is discussed that adiponectin might be involved in the chronic cardiac insufficiency (CCI) pathogenesis. A study performed by Kreth et al., characterized the adiponectin and its receptors expression in CCI to evaluate the impact of microRNAs in the cardiac adiponectin system. In CCI, AdipoR1 cardiac expression was four-fold increased, while the AdipoR2 increase was two times lower, showing the adiponectin association with its receptors in the heart and that the microRNA-150 targeting might be a strategy to restore the cardioprotective adiponectin effects [99].

1.3.2. Leptin

Establishing the association between leptin and Ang-(1–7), a study performed by Uchiyama et al., investigated the perirenal visceral adipose tissue and visceral perirenal adipocyte isolated from Wistar male rats. The authors observed that Ang-(1–7) increased leptin secretion and expression, while alamandine decreased the leptin secretion and expression in the adipose tissue and serum [100]. Few studies are presenting the relation between leptin and Ang-(1–7), and among them, Schuchardet et al. demonstrated the Ang-(1–7) potential in regulating rats food intake and body weight. Ang-(1–7) also contributes to weight loss following AT1R blockage, since transgenic rats remained leptin responsible even with a chocolate and cookie diet. It is also suggested that Ang-(1–7) agonists might be pharmacological candidates in the obesity treatment and a new tool to treat metabolic disorders [101].

Mas double deficiency in ApoE-KO (DKO) mice leads to a lipodystrophy similar state, with increased hepatic lipid content and increased alanine aminotransferase levels. It was also observed increased cholesterol, triglycerides, and fasting glucose levels and decreased HDL and leptin levels [102].

Hamrick showed that leptin treatment in vivo increases myogenic genes expression in mice primary myoblasts. Leptin may centrally reduce medullar adipogenesis via its receptors in the hypothalamus, as well as directly through their receptors on bone marrow stem cells. Thus, aging seems to significantly alter the crosstalk mediated by leptin among organs and tissues [103].

The renal dysfunction in the chronic renal disease context is associated with high leptin levels, that also in NAFLD causes activation of renal mesangial cells and tubular inflammation via a NOX2 dependent pathway that positively regulates the pro-inflammatory miR21 molecule, findings from a mice model [104,105]. The Ang-(1–7)/MasR axis in the mice kidneys have vasodilatory, antiproliferative, antidiuretic and antinatriuretic activities [106,107].

In the heart, Carmo et al. recently determined that neuronal-SOCS3 deficiency in mice is a potential negative regulator of the leptin signaling pathway that amplifies the chronic leptin effects on food intake, energy expenditure, glucose and arterial pressure, protecting against the adverse cardiometabolic effects in obesity [108]. Oral administration of alamandine generated antihypertensive and antifibrotic effects in rats [109]. Furthermore, its subcutaneous application also exerted antihypertensive effects, with improved cardiac hypertrophy and left ventricle function. Alamandine may exert its beneficial effects via the protein kinase A (PKA) signaling pathway modulation [110]. Interestingly, Wang et al. showed in rats that leptin is also produced by the skeletal muscle, and the leptin receptors are abundant in skeletal muscle and mesenchymal stem cells derived from bone (stroma), thus confirming this adipokine effects on the muscle cells [111].

The leptin influence on the human cardiovascular system and adipose metabolism has also been investigated and the main findings evidence a positive leptin effect produced by the pericardial adipose tissue and blood vessels [112]. An interesting study performed by Oral et al. showed that leptin administration in nine women with lipodystrophy and leptin serum levels below 4 ng/mL, significantly improved lipodystrophy besides insulin resistance [113].

1.3.3. Resistin

It was shown that Ang-(1–7) oral treatment improved the obese rats' metabolic profile (improved body weight, abdominal fat mass, insulin plasma levels, and circulating lipid levels) via decreased resistin, TLR4, ACE and increased ACE2 expression in the liver [72]. Santos and colleagues showed that Ang-(1–7) decreases MAPK phosphorylation, reducing IL-6 and TNF-α expression via resistin/TLR4/NF-kβ-pathway down-regulation in rats [72].

Resistin levels are increased in obesity. In a study performed in high-fat-fed mice, the resistin levels normalization by antisense oligonucleotides reverses hepatic insulin resistance [114,115]. These proteins supposedly contribute to the visceral adiposity deleterious metabolic effects. Increased insulin secretion was observed in mice MasKO pancreatic islets treated with A776 (Mas antagonist) and stimulated with Ang-(1–7), although the insulin expression was not altered, indicating a smaller Ang-(1–7) not exclusively by Mas-dependent pathways [116].

Translational studies that investigated the resistin role in humans reported interesting findings. First, resistin expression was shown to be increased in fibrotic liver. In hepatic stellate cells, resistin seems to increase MCP-1 and interleukin-8 (IL-8) expression [117], besides contributing to the lipids uncontrolled uptake. The hepatic low-density lipoprotein receptor (LDL) negative regulation and de novo lipogenesis stimulation in hepatic cells are triggered by resistin and may augment dyslipidemia and hepatic steatosis [118].

In the pancreatic islets on the other hand, the literature regarding the resistin expression is scarce [119]. However, Alexandra et al. showed the resistin expression in human pancreatic islets via qRT-PCR and immunohistochemistry shedding new light on the resistin potential role in the pancreas [119].

Second, regarding the relationship between inflammation and the adipokines, Hollebeke et al. studied the abdominal muscular density and area with inflammatory mediators associated with adiposity and resistin. The results showed that the muscular area was not associated with any inflammatory mediators studied, including resistin. It was yet not verified that higher densities of several muscle groups in the abdomen are significantly associated to lower IL-6 and resistin levels, independent from the muscle area in these groups [120].

Lastly, in the cardiovascular system, resistin levels are associated with coronary artery disease and heart failure severity. Turgay et al. evaluated if there is a relation between resistin levels and final diastolic pressure in the left ventricle and observed no correlation between resistin levels and left ventricular-end diastolic pressure, coronary artery disease severity, echocardiographic diastolic dysfunction parameters and constraint induced movement therapy. More studies are necessary to evaluate the resistin efficacy for clinical use [121].

1.3.4. Omentin

The association between omentin and Ang-(1–7) is still unknown in the literature, becoming a potential target for new studies. Omentin is an anti-inflammatory protein and improves insulin sensitivity [122]. If the omentin directly regulates the hepatic cells, biological function is still not clear in the literature. Unbalanced nitric oxide levels contribute to splanchnic vasodilation and hepatic vasoconstriction and consequently portal hypertension [123]. Although several mechanisms influence the vasodilation process, the RAS is one of the most studied over the years, and it is discussed that the ACE/Ang II/AT1 axis has been intimately associated with cardiovascular dysfunctions and metabolic disturbances [124].

Sit et al. evaluated the inflammatory response effects on serum omentin levels in acute and chronic pancreatitis and found that omentin levels elevation in rats at the early stage of pancreatitis was due to omentin's anti-inflammatory effects [125]. Castro et al. showed that both adipose tissue metabolism and adipokine secretion might be affected in diabetic rats, but omentin was no different between the groups [126].

The omentin role in human studies are more focused on metabolic diseases, where it was evidenced decreased omentin levels in type 1 and 2 diabetes *mellitus*, correlating with insulin resistance [127,128], which might be explained by the strong relationship between arterial pressure and insulin plasma concentration in hypertensive individuals with obesity, acting not only in the sympathetic nervous system, but also in renal function and arterial walls, leading to increased arterial pressure [129].

Moreover, Zorlu et al. compared serum omentin and obestatin levels in type 2 diabetic patients with normoalbuminuria and macroalbuminuria and observed that higher obestatin serum levels were associated with macroalbuminuria, whereas serum omentin levels were similar between groups suggesting that obestatin may play a role in the underlying pathogenic mechanisms leading to diabetic nephropathy [130].

In the cardiovascular context, Fernándes-Trasancos et al. evaluated the omentin effects on the epicardial adipose tissue and vascular cells. This study showed that omentin treatment increased adiponectin levels induced by adipogenesis and reduced TNF-α levels in mature adipocytes. Omentin improved insulin activity in EAT and subcutaneous adipose tissue explants from patients with cardiovascular disease and decreased smooth muscle cells migration [131]. It is observed in the literature that omentin positively associates with adiponectin [129], which may justify the inflammation attenuation in the epicardial adipose tissue via ACE/Ang-(1–7)/Mas that reduces obesity-induced cardiac dysfunction by increasing adiponectin levels.

1.3.5. Apelin

Recently, Sabry et al. assessed the apelin treatment effects on diabetes *mellitus* type 2 induced by obesity and the possible interaction between the apelin/APJ and the renin-angiotensin system. The study showed that apelin-13 administration in rats resulted in improved insulin resistance, dyslipidemia, inflammation, oxidative stress, reduced AT1 gene expression and increased ACE2 expression in the adipose tissue, evidencing that the apelin beneficial effects are NO/ACE2/Ang-(1–7) dependent [132].

A review showed that apelin is the second catalytic substrate for ACE2 and acts as an inotropic and cardiovascular protective peptide. Chen et al. showed that microRNAs, linked to ACE2/apelin modulation, exhibit beneficial effects in the cardiovascular system and hypertension. The crosstalk between ACE2, the apelin system and microRNAs provides an important hypertension mechanist view [133]. Another review of the literature evidenced that the Apelin/APJ system is mainly expressed in vascular smooth muscle cells (VSMC). The study by Luo et al. was the first to demonstrate that the apelin/APJ system increases the VSMC proliferation by the extracellular signal–regulated kinase 1 (ERK1)/2-cyclin D1 signal pathway, thus being a promising target for the management of the vascular disease management [134]. The apelin effects on the cerebral arteries are unknown. Mughal, Sun and, O'Rourke, have demonstrated that apelin reduces the cerebral arteries nitric oxide-induced relaxation by inhibiting the calcium-activated high-conductance K channels activation [135].

Recently, it was showed that the apelin/APJ system develops a critical role in kidney disease [136]. Guo et al. verified in mice that this system induces podocyte dysfunction in diabetic nephropathy via endoplasmic reticulum stress induced by decreased proteasome activity in podocytes [137]. In this sense, the apelin-APJ system, in animal models, develops diverse roles in renal disease and might be a potential target in the renal disease treatment [138].

The inflammation develops an essential role in pancreatitis, and thus, Hans et al. showed that apelin inhibited the positive regulation of TNF-α, MIP-1α/β and IL-1β in mice with chronic pancreatitis, thus evidencing that apelin is involved in the inflammatory mediator's modulation in pancreatitis in this animal model [139].

The human studies involving the investigation of the apelin role on the other hand, are mainly focused on metabolism. It was reported that the physical exercise beneficial metabolic effects might be mediated by myokines. In this sense, Besse-Patim et al. studied the physical training effects and apelin expression in the human skeletal muscle. It was observed that physical training increases apelin expression in an obese individual via exercise-induced signaling pathways, thus being considered a new myokine with autocrine and paracrine actions. The physical activity beneficial effects on reducing arterial pressure in

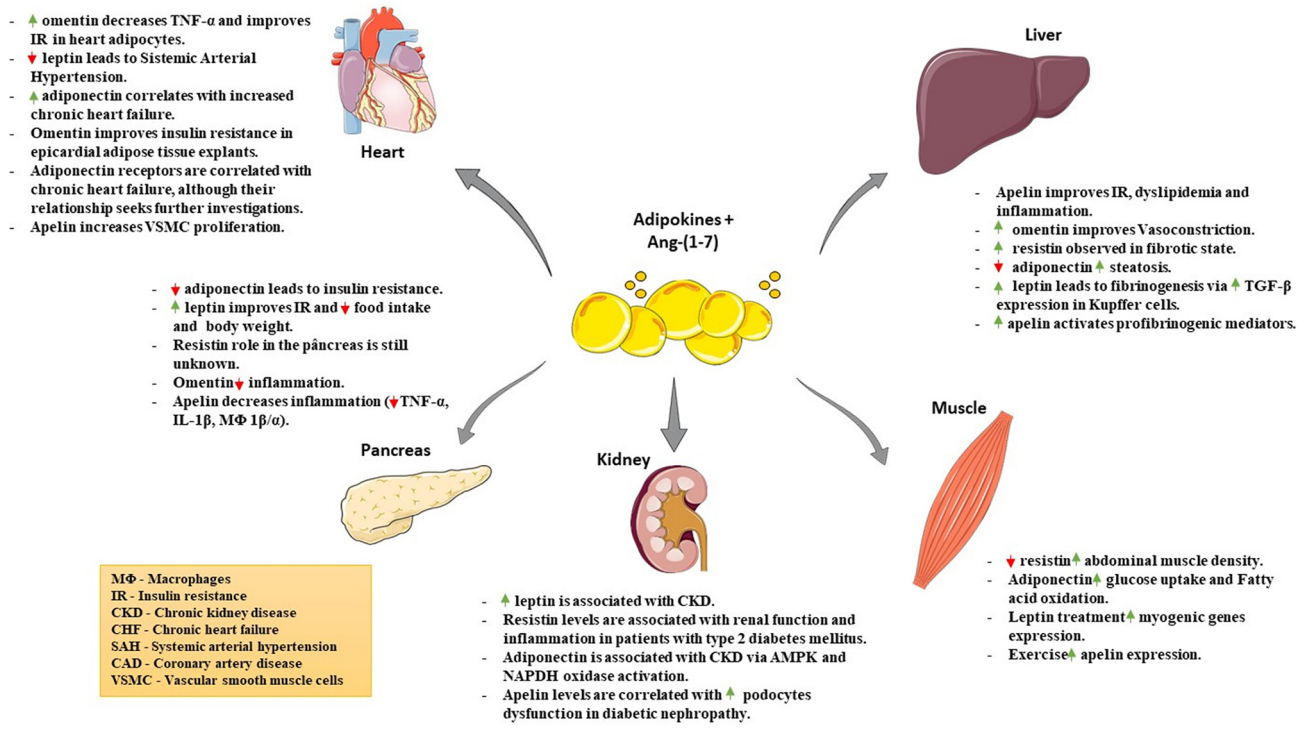

Fig. 3. Ang- (1–7) effects on adipokines: Ang-(1–7) has a protective effect despite the relationship between omentin and Ang-(1–7) being unknown. In the liver, the decrease of Adiponectin and increase of the other adipokines contribute to deleterious effects. In the pancreas there is an opposite effect to the liver and little is known about the effects of resistin. In the muscle, the decrease in resistin leads to an increase in abdominal muscle density and the increase in other adipokines has beneficial effects. Little is known about the impact of omentin on muscle. In the kidneys, the rise in adipokines contributes to the adverse effects. In the heart and blood vessels, the apelin/APJ system increases the proliferation of vascular smooth muscle cells while the other adipokines do not have favorable effects.

hypertensive individuals are linked, at least in part, to an increased apelin/APJ system expression. [140].

Interestingly, in vitro experiments with human cells evidenced that the angiotensin-converting enzyme 2 (ACE2) is a counterproductive regulator of the renin-angiotensin system (RAS), catalyzing the conversion of Ang II to Ang-(1–7). The apelin is a second catalytic substrate for ACE2 and functions as an inotropic peptide and cardioprotective [141]. Although an antagonistic relationship has been proposed between RAS and apelin, this functional interaction remains uncertain.

In this perspective, we may conclude that adipokines, produced by the adipose tissue, have paracrine and autocrine actions that thus exert an effect in several organs and consequently different physiological and pathophysiological conditions (Fig. 3). These observations and evidence highlight the adipokines importance as molecular targets to be modulated in metabolic diseases treatment and prevention.

2. Adipokines and clinical implications

According to the Global report on diabetes from the World Health Organization, the diabetes prevalence almost quadrupled since 1980, reaching 422 million adults, which is in great part, due to the increased overweight/obesity (considered the main diabetes type 2 risk factor) prevalence. Type 2 diabetes *mellitus* may lead to macro and microvascular complications, and in 2012, was the direct death cause of 1.5 million people [142]. This growing prevalence and mortality generate social and economic implications in the health systems globally. It is necessary to find therapeutic targets aimed to set not only type 2 diabetes *mellitus* treatments but also risk factors attenuation [143]. In this context, deepening the knowledge of the adipokines endocrine effects in different target organs, their signaling pathways and links with RAS may contribute to developing new drugs, aiming at the diseases associated with broad-spectrum obesity therapy.

In obesity and type 2 diabetes *mellitus*, insulin resistance affects the perivascular adipose tissue endocrine function, altering vasoconstrictor and vasodilator molecules secretion and increasing the oxygen reactive species production. A study demonstrated that plasma adipokines or their receptors expression might improve insulin sensitivity and reduce cardiometabolic diseases morbimortality. In this perspective, the adipokines may constitute potential therapeutic targets for obesity and type 2 diabetes *mellitus* [144,145]. A study investigated the association between adipokines, anthropometric measures and biochemical parameters in type 2 diabetes *mellitus*, demonstrating that central obesity is correlated with adipokines synthesis unbalance, reinforcing their importance in type 2 diabetes *mellitus* [146]. Besides that, adipokines may be considered clinical biomarkers for the diagnosis and early interventions in pre-diabetic and T2DM patients [147].

Although several studies point to physiological and pathophysiological Ang-(1–7) properties in type 2 diabetes *mellitus* progression, its protective effects against hyperglycemia damage are still not completely elucidated. A clinical study also showed that intra-arterial infusion of Ang-(1–7) in obese patients exerted favorable effects by stimulating insulin-triggered vasodilation and inhibiting endothelin-1 vasoconstriction, which are comorbidities associated with obesity and insulin/glucose impaired metabolism [148].

Interestingly, a phase II, open-label pilot study reported that ACE2 infusion in patients with pulmonary arterial hypertension improved pulmonary hemodynamics and reduced oxidative stress and inflammation [149]. This study exemplifies the clinical application of RAS modulation in ameliorating disorders, such as hypertension. Recombinant ACE2 infusion in healthy individuals was also evaluated. The treatment was well tolerated and lead to significant changes in the RAS peptides concentrations [150].

Studies performed with animal models demonstrated that adiponectin exerts a fundamental role in obesity-associated diseases pathophysiology. Acting through its receptors (AdipoR1 and AdipoR2), it exerts direct effects on the liver, skeletal muscles, and vasculature (metabolic tissues), improving insulin sensitivity, lipid profile and producing anti-atherogenic and anti-inflammatory effects [151–154].

Leptin regulates energy homeostasis by inhibiting hunger (anorexigenic) and by increasing energy expenditure in over food conditions and increased fatty acid uptake. Leptin receptors are distributed in peripheral tissues, but the central nervous system is considered the main ingestion regulation site, which occurs via neurotensin (neurotransmitter). Recent findings demonstrated a positive association between circulating leptin and neurotensin, broadening the leptin-neurotensin peripheral and central mechanisms understanding, with new therapeutic approaches perspectives [155].

Resistin was primarily known as a hormone secreted by adipocytes, but it is mainly expressed and secreted by macrophages. Increased resistin levels are associated with insulin resistance, endothelial dysfunction, and smooth muscle cells proliferation, promoting type 2 diabetes *mellitus* and mediating atherosclerosis pathogenesis [156]. Hepatic biopsies have shown that resistin plays an important role in the hepatic insulin resistance pathogenesis, aggravating NAFLD, being the most significant expression in patients with T2DM and dyslipidemia [157].

Apelin exerts significant effects on glycaemic and lipid metabolism, and it is mainly expressed and released by adipocytes. The apelin injection stimulated glucose uptake by the adipose tissue in mice and human [158,159]. Additionally, exogenous apelin administration in patients with central obesity resulted in insulin-stimulated vasodilation, thus showing the apelin effects on hemodynamic alterations associated with insulin impaired function conditions such as obesity [160].

Recently, ghrelin has been associated with several significant effects, besides its contribution as an orexigenic hormone, acting in the systemic metabolism. The ghrelin agonism may offer a therapeutic possibility for diabetic gastroparesis and anorexia, and its receptor antagonism may be used in the treatment of obesity and to improve glycaemic metabolism and type 2 diabetes *mellitus* [161,162].

3. Concluding remarks

In summary, it is important to highlight the adipose tissue endocrine significance on synthesizing adipokines, modulating its secretion and regulating several processes associated with acute and chronic inflammation, besides its relevance in whole body homeostasis. In the present review, we evidenced the main adipokines participation and their interaction with inflammation and the ACE2/Ang-(1–7)/MasR RAS axis. The molecular pathways involved in the adipokines action mechanisms raised the need for new studies aiming to investigate therapeutic interventions, as well as new tools to clarify the unknown mechanisms. The Ang-(1–7) interaction and relevance on the adipokines expression and inflammation were discussed in obesity, type 2 diabetes, cardiovascular diseases, renal and hepatic disorders, among others. In this perspective, we concluded that inflammation may be modulated by adipokines and Ang-(1–7) in different organs and might be an important target for the treatment and prevention of inflammatory responses.

Conflicts of interest

The authors declare no conflicts of interest.

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