ANGIOTENSIN-(1-7): AN ANTI-INFLAMMATORY AND PRO-RESOLUTIVE PEPTIDE

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ABSTRACT
In recent decades the renin-angiotensin system has been established itself as a complex regulatory mechanism composed of different pathways involved in the control of physiological functions and, when for long term inappropriately activated, it is involved in the pathophysiology of different diseases. Among its biologically active peptides, angiotensin-(1-7) and its receptor Mas, represent an important counter-regulatory mechanism due to their antihypertensive, anti-inflammatory, anti-proliferative and antifibrotic effects. In this review, we present data that besides demonstrating the antiinflammatory effect, indicate that angiotensin-(1-7) has a crucial additional effect on the return to tissue homeostasis, that is to promote resolution of the inflammatory process. These studies point angiotensin-(1-7) or activation of Mas receptor as important therapeutic targets for the treatment of inflammatory diseases.
Keywords: Renin-angiotensin system, Angiotensin-(1-7), Mas receptor, Inflammation, Resolution, asthma, arthritis

RESUMEN
En las últimas décadas, el sistema renina-angiotensina se ha establecido como un mecanismo regulador complejo compuesto de diferentes vías involucradas no solo en el control de funciones fisiológicas sino también en la fisiopatología de diferentes enfermedades cuando se activa de manera inapropiada y a largo plazo. Entre sus péptidos biológicamente activos, la angiotensina-(1-7) y su receptor Mas representan un mecanismo contrarregulador importante debido a efectos antihipertensivos, antiinflamatorios, antiproliferativos y antifibróticos. En esta revisión presentamos datos que, además de demostrar el efecto antiinflamatorio, indican que la angiotensina-(1-7) tiene un efecto adicional crucial en el retorno a la homeostasis del tejido, que es promover la resolución del proceso inflamatorio. Estos estudios apuntan a la angiotensina-(1-7) y/o la activación del receptor Mas, como importantes blancos terapéuticos para el tratamiento de enfermedades inflamatorias.
Palabras clave: Sistema Renina-Angiotensina, Angiotensina-(1-7), Receptor Mas, Inflamación, Asma, Artritis

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Renin-angiotensin system

The renin-angiotensin system (RAS) is considered one of the most important regulatory systems to maintain cardiovascular and hydroelectrolytic homeostasis. Its influence on cardiovascular and renal functions is extremely broad and complex, as it involves multiple mediators, receptors and various intracellular signaling mechanisms [1]. Classically, the RAS is considered a circulating hormonal pathway where a liver-released α-glycoprotein angiotensinogen, is hydrolyzed in the circulation by a renin aspartyl protease secreted by the juxtaglomerular cells of the kidneys, forming angiotensin I (Ang I). Angiotensin-converting enzyme (ACE), a metalloproteinase present in the endothelium, removes two C-terminal amino acids (His-Leu) from Ang I forming the octapeptide Ang II, considered the major active peptide of RAS (1). However, studies in recent decades have demonstrated that other biologically active peptides, including Ang(2-8) (Ang III), Ang-(3-8) (Ang IV), Ang-(1-7), Ang-(1-12), Ang-(1-9) and alamandine can be formed both in the circulation and in the tissues [1,2]; **(Figure 1)**.

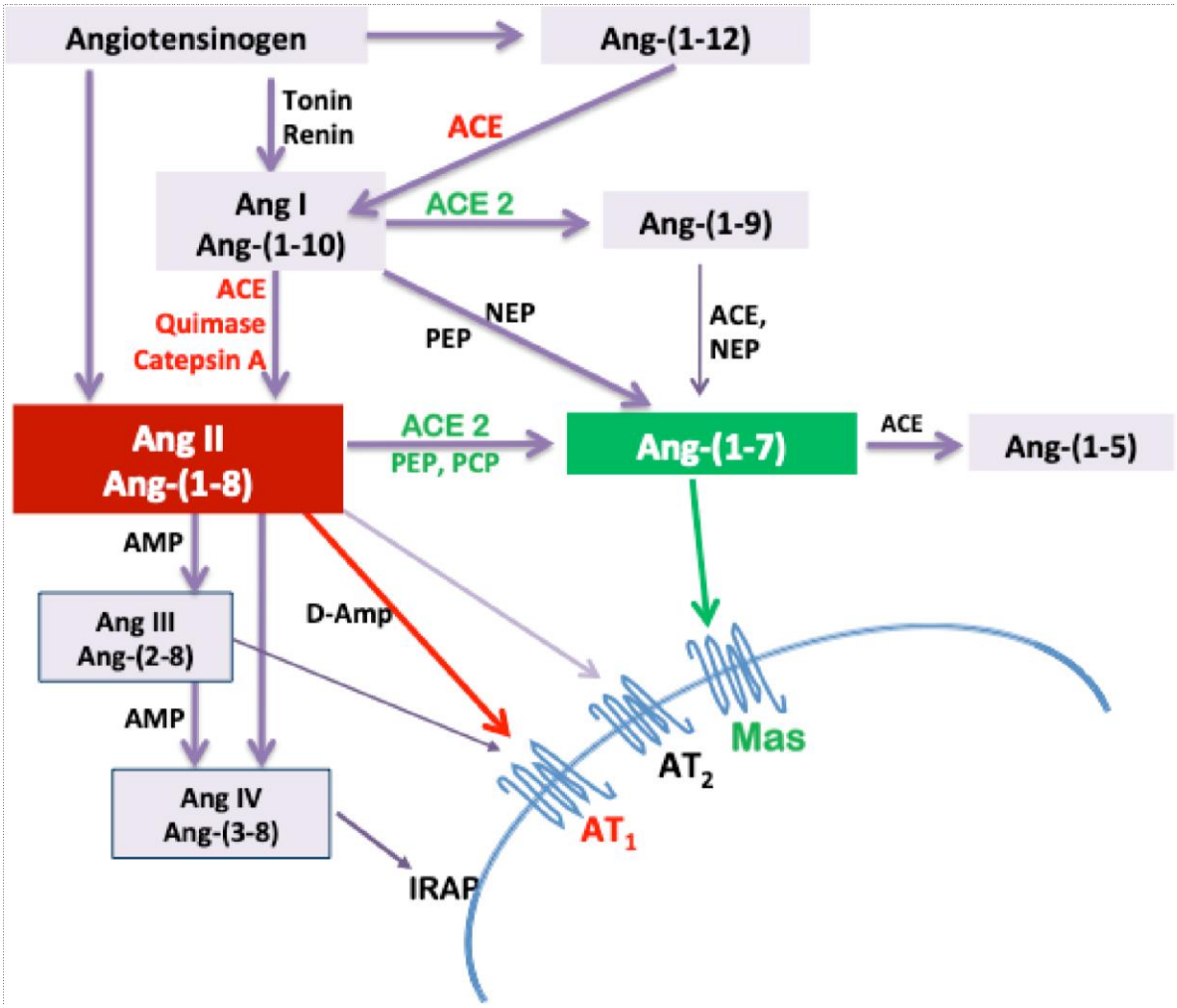

Figure 1. Pathways of formation of peptides of the renin-angiotensin system and main receptors. ACE: Angiotensin Converting Enzyme; AMP: Aminopeptidase; AT: Angiotensin Receptor; Ang: angiotensin; IRAP: Insulin-Regulated Aminopeptidase; NEP: Neutral Endopeptidase; PCP: Prolyl-carboxypeptidase; PEP: Prolyl Endopeptidase.

In 1988, Santos and colleagues working at the Cleveland Clinic Foundation, OH, USA and investigating the in vitro metabolism of radioisotope-labeled Ang I in dog brainstem homogenates, showed that, although Ang I was metabolized to Ang II, the major product of Ang I metabolism was the heptapeptide, Ang-(1-7), both in the absence and presence of an ACE inhibitor [3]. Following this result, colleagues from the same laboratory demonstrated in hypothalamus-neurohypophysis explants that Ang-(1-7) could stimulate the release of vasopressin [4]. In addition, Ang-(1-7) was shown to be present in several forebrain structures, such as the paraventricular, supraoptic and suprachiasmatic nuclei of the hypothalamus, terminal striatum, innominate substance, medial eminence and neurohypophysis [5]. In the following year, Campagnole-Santos and colleagues (1989) showed that the microinjection of Ang-(1-7) into the nucleus of the rat solitary tract induced bradycardia and hypotensive effects [6]. These data led to the conclusion that Ang-(1-7) could be a neuromodulator and opened a new possibility of action for the RAS. Several studies developed in different laboratories around the world were followed and characterized the physiological role of Ang-(1-7), not only in the brain, but also in different organs/ tissues [1]. Interestingly, this alternative route of the RAS involved a homologous ACE enzyme, ACE2, which was discovered in 2000 by two distinct researcher groups [7,8]. ACE2 has emerged as a potent negative regulator of the RAS, since it cleaves one amino acid from the carboxy-terminal of Ang II producing Ang-(1-7).

Only in 2003, nearly 15 years after the first descriptions of Ang-(1-7) actions, Santos and colleagues demonstrated that its effects were mainly mediated by the orphan G protein-coupled receptor, Mas [9]. Most of the effects described for Ang-(1-7) are opposite from those observed for Ang II. The RAS is currently recognized as a complex peptidergic system which role mainly depends on the balance between the activity of two opposite pathways: ACE/ Ang II/ receptor AT_1 and ACE2/ Ang-(1-7)/ Mas receptor [1]. The balance of these pathways is important for the control of blood pressure and hydroelectrolytic balance, but, when unregulated and favoring activation of Ang II/ AT1 receptor, is involved in the pathophysiology of different diseases [1,10].

There is experimental and clinical evidence indicating that activation of the RAS is involved in the pathophysiology of inflammation and tissue remodeling, especially through an inappropriate increase in ACE/ Ang II/ AT_1 receptor [10]. On the other hand, studies have shown that ACE2/ Ang-(1-7)/ Mas receptor axis activation could play a protective role in the context of inflammation [10]. Data suggest a promising new therapeutic pathway to be investigated in inflammatory diseases, especially when traditional treatments fail to promote resolution of the inflammation or when there is no cure.

ECA2/ Ang-(1-7)/ Mas: Anti-inflammatory effects

Inflammation is a physiological response of the immune system to cellular and tissue damage caused by various types of agents. Important events occur during the inflammatory process, including increased vascular permeability, recruitment, adhesion, and migration of leukocyte to the site of inflammation, production and release of inflammatory mediators [11]. After elimination of the harmful agent, the inflammatory process must be resolved. Resolution of the inflammatory process is characterized by (*i*) production of mediators that prevent excessive leukocyte trafficking; (*ii*) shutdown of intracellular signaling molecules associated with cytokine production and leukocyte survival; (*iii*) induction of apoptosis of recruited inflammatory cells and (*iv*) elimination of apoptotic cells, especially by macrophages by a non-phlogistic process. All these processes allow termination of inflammation and the

restoration of tissue homeostasis [12]. Failure to resolve inflammation underlies a variety of chronic inflammatory diseases [13].

Studies have demonstrated an anti-inflammatory effect of Ang-(1-7) in several experimental models [10]. In these studies, administration of Ang-(1-7) decreased production of inflammatory mediators, leukocytes adhesion/migration and activation of cellular signaling pathways involved in leukocyte survival and cytokine and chemokine production [10]. In keeping with Ang-(1-7) actions, Mas receptor has been detected in several cells of the immune system, such as, dendritic cells [14], lymphocytes [10], macrophages [15], eosinophils [16], neutrophils [17], microglia [18] and alveolar macrophages [19]. Cells in different tissues, such as, epithelium and airway smooth muscle [20] and alveolar cells [19], vascular smooth muscle cells, endothelium and cardiomyocytes [21], choroid plexus endothelium and various central nervous system cells [21,22], spleen, renal cells [21], among others, also express the Mas receptor. The identification of Mas receptor in these cells and tissues indicates a mechanism for Ang-(17) actions.

In models of pulmonary inflammation, such as asthma [16,20,23-25], lung fibrosis, pulmonary hypertension [26] and emphysema [27,28], treatment with Ang-(1-7) decreased cytokine/chemokine synthesis and migration of inflammatory cells to the lung (**Figure 2)**.

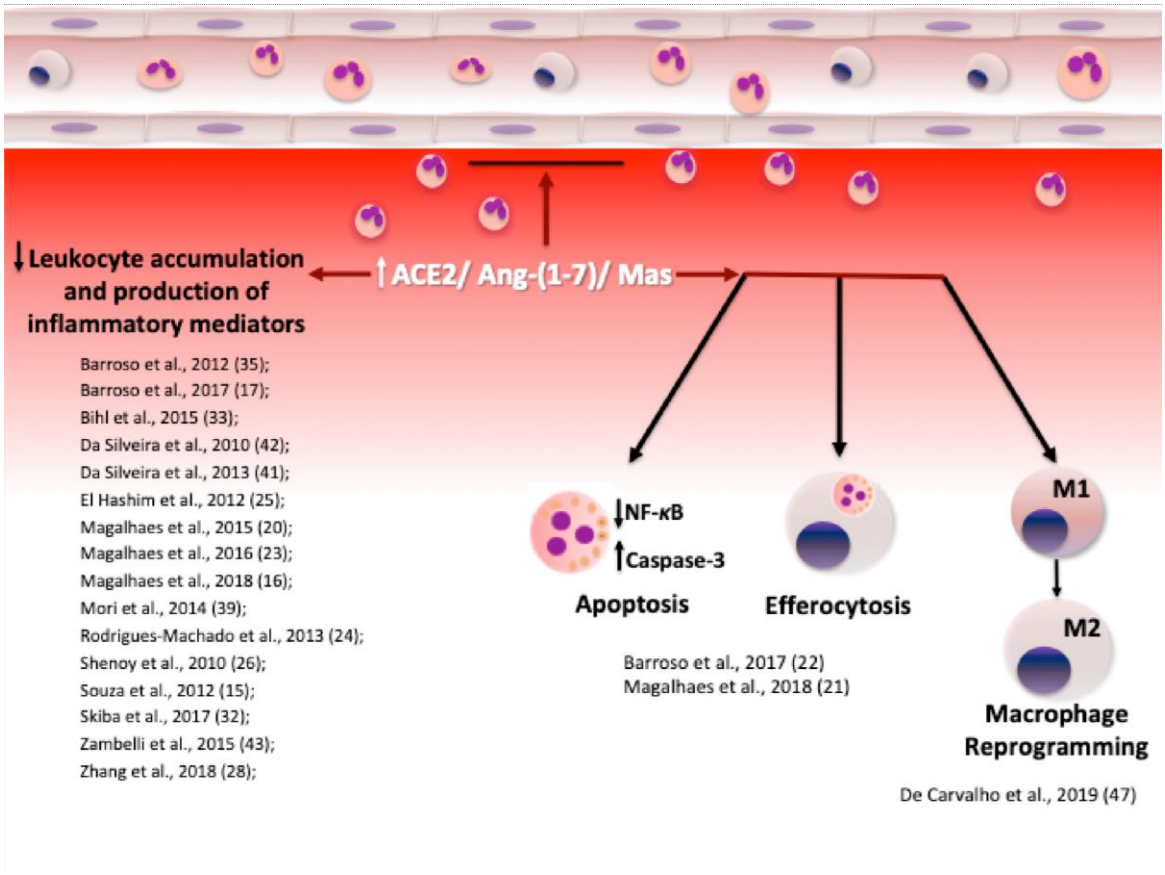

Figure 2. Main angiotensin-(1-7) effects in inflammation. Inflammation initiates with the production of proinflammatory mediators and activation of survival signal pathways. Several studies showed that angiotensin-(1-7) reduces the release of inflammatory mediators and the accumulation of leukocytes in the inflammatory site. These actions are important to minimize tissue and organ damage. Ang-(1-7) decreased cell survival pathways and activated granulocyte apoptosis. Ang-(1-7) was also capable of increasing efferocytosis and coordinate macrophage reprogramming. Altogether data show that angiotensin-(1-7) promotes pro-resolutive events reestablishing tissue homeostasis.

In an experimental murine model of allergic asthma induced by ovalbumine sensitization and challenge, treatment with Ang-(1-7) reduced the increased production of proinflammatory cytokines related to activation of T helper 2 type immune response. In addition, reduced chemokines and the number of leukocytes in the lung, especially eosinophils. Ang-(1-7) also decreased NF-κB and ERK1/2 phosphorylation in the lung of asthmatic mice [20,25]. These events prevented and attenuated tissue remodeling and kept lung functionality [16,20,24,25]. The beneficial actions mediated by Ang-(1-7) in the allergic lung inflammation models were shown to be dependent on activation of Mas receptor. Accordingly, chronic asthma was aggravated in Ang-(1-7) Mas receptor knockout mice [23,24]. Thus, impairment of the Ang-(1-7)/Mas receptor pathway may lead to deterioration of the pathophysiology of asthma.

In lung fibrosis and pulmonary hypertension the ECA2/Ang-(1-7)/Mas activation decreased the levels of TGF-β, TNFα, IL-6 , IL-1β and lung fibrosis [26]. In a pulmonary model of emphysema induced by elastase administration, treatment with an oral formulation of Ang-(1-7) reduced lung IL-1β, increased the anti-inflammatory cytokine, IL-10, and restored alveolar tissue area [27]. Further, cigarette smoke-induced chronic obstructive pulmonary disease in mice was attenuated with Ang-(1-7) treatment [28]. In this study, Ang-(1-7) reduced IL-6, TGF-β, TNF-α, the number of leukocytes and NF-κB phosphorylation in the lung [28].

In the cardiovascular system, Ang-(1-7) also exerts anti-inflammatory actions [10]. In experimental myocardial infarct model, Ang-(1-7) oral treatment improved cardiac function and reduced TGF-β and collagen type I expression [29]. In addition, Ang-(1-7) led to downregulation of CXCR4, which can be a therapeutic target for ischemic heart diseases [30]. Cardiac effects were also observed after lateral cerebral ventricle (ICV) treatment with Ang-(1-7), which was shown to reduce collagen I, fibronectin and TGF-β in the heart of hypertensive rats [31]. These effects were associated with improvement of heart function, attenuation of blood pressure and restoration of cardiac autonomic balance [31]. In another model, activation of Mas receptor inhibited perivascular inflammation by reducing IL-1β, TNF-α, CCL2 and CXCL10 expression in perivascular adipose tissue through inhibition of macrophage differentiation into the inflammatory type, M1 [32]. Anti-inflammatory effects mediated by Ang-(1-7) have also been described in stroke [33,34]. For example, treatment with Ang-(1-7) in hemorrhagic stroke induced downregulation of NFκB and decrease in TNF-α, MCP-1 and IL-8 [33]. Evidences that the ACE2/ Ang-(1-7)/ Mas axis can modulate inflammation have also been described in other experimental models, such as, hepatic fibrosis, renal injury, diabetic nephropathy, arthritis and autoimmune encephalomyelitis [35-43].

ECA2/ Ang-(1-7)/ Mas: Pro-resolutive effects

The role of Ang-(1-7) in the resolution of inflammation has been demonstrated in asthma and arthritis murine models [16,17]. Both are chronic, disabling diseases whose current treatment does not alter its progression, posing a major challenge for the public health system. Current therapies are aimed to reducing inflammation and symptoms [44,45]. Studies show that failure of eosinophilic and neutrophilic resolution is the main reason for chronicity and loss of organ function in asthma and arthritis, respectively [44,45]. Thus, reduced apoptosis of eosinophils and neutrophils, as well as failure of elimination of apoptotic cells by phagocytes, a process called efferocytosis, are key mechanisms for the defective resolution found in asthma and arthritis [44,45].

In asthma, Ang-(1-7) treatment at the peak of eosinophilic inflammation induced eosinophil apoptosis and NF-kB activation in these cells and in the lung. In addition, Ang(1-7) reduced ERK1/2 phosphorylation and GATA3 expression, this later an essential transcription factor for Th2-driven inflammation. Therefore, resolution of inflammation induced by Ang-(1-7) was not only associated with apoptosis of eosinophils but also with decrease in Th2 response, which is important for the development and prolongation of the disease. In this study, treatment with Ang-(1-7) at the peak of eosinophilic inflammation also reduced the expression of collagen type I and II in the lung [16].

In an arthritis model, Ang-(1-7) treatment at the peak of neutrophilic inflammation induced caspase-dependent neutrophil apoptosis and inhibition of NF-κB [17]. Mas receptor blockade with A779 antagonist inhibited the pro-resolutive effects mediated by Ang-(1-7) and delayed natural resolution. Moreover, Ang-(1-7) induced apoptosis of human neutrophils, an effect associated with NF-κB inhibition [17]. It is important to point out that the reduction in eosinophils and neutrophils observed with Ang-(1-7) treatment in asthma [16] and arthritis [17], respectively, was not accompanied by a reduction in mononuclear cells. For example, in the ovalbumin-induced asthma model, Ang-(1-7) treatment at the peak of eosinophilic inflammation increased caspase 3 expression in lung recruited macrophages, but not in alveolar macrophages [16]. These results indicate that Ang-(1-7) activates apoptotic death events in the target inflammatory cells, without altering survival of mononuclear cells, which enable these cells to remove apoptotic leukocytes by efferocytosis.

Ang-(1-7) action on efferocytosis was studied in a classic in vivo model [16,17]. In this model, peritonitis is induced in mice by zymosan administration. Three days later, animals received Ang-(1-7) and, 30 min after, human polymorphonuclear (PMNs) apoptotic cells. Mice were killed after 3h and exudates were collected for morphologic analysis of the percentage of macrophages containing apoptotic PMNs. Treatment with Ang-(1-7) induced a significant increase in efferocytosis of apoptotic PMNs cells [16,17]. Resolutive molecules are also able to promote efferocytosis and coordinate reprogramming of macrophages [46]. More recently, Ang-(1-7) has been shown to promote antiinflammatory responses in macrophages [47]. In this study Ang-(1-7) promoted the reduction of macrophages with inflammatory characteristics (M1) and enhanced the reprogramming of M1 to M2 macrophages, anti-inflammatory mediators [47].

In summary, increasing evidence show that Ang-(1-7) is an anti-inflammatory and pro-resolutive mediator (**Figure 2**). The studies available reinforce the importance to develop new therapies based on Ang-(1-7) or Mas receptor activation to more effectively treat acute and chronic inflammatory diseases.

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