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The Angiotensin-(1-12)/Chymase Axis as an Alternate Component of the Tissue Renin Angiotensin System

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Abstract

The identification of an alternate extended form of angiotensin I composed of the first twelve amino acids at the N-terminal of angiotensinogen has generated new knowledge of the importance of noncanonical mechanisms for renin independent generation of angiotensins. The human sequence of the dodecapeptide angiotensin-(1-12) [N-Asp^{1}-Arg^{2}-Val^{3}-Tyr^{4}-Ile^{5}-His^{6}-Pro^{7}-Phe^{8}-His^{9}-Leu^{10}-Va^{l1}-Ile^{12}-COOH] is an endogenous substrate that in the rat has been documented to be present in multiple organs including the heart, brain, kidney, gut, adrenal gland, and the bone marrow. Newer studies have confirmed the existence of Ang-(1-12) as an Ang II-forming substrate in the blood and heart of normal and diseased patients. Studies to-date document that angiotensin II generation from angiotensin-(1-12) does not require renin participation while chymase rather than angiotensin converting enzyme shows high catalytic activity in converting this substrate into angiotensin II directly.

Keywords

Renin-angiotensin system; angiotensinogen; angiotensin peptides; angiotensin-(1-12); angiotensin I; angiotensin II; renin; chymase; angiotensin-converting enzyme; renin; metabolism

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Disclosure

Authors declare that there are no potential conflicts of interest relevant to this article.

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Introduction

It has been widely addressed in the literature that the central role of the circulating renin-angiotensin system (RAS) is to maintain blood pressure and body fluid homeostasis (Yim and Yoo, 2008, de Souza, West, de Abreu et al., 2018). In addition to its role as an endocrine system, data demonstrates the presence of genes and proteins of the system within the interstitial spaces of the extracellular environment and the membranes, organelles and nuclei of the cells itself (Leung, 2010,Jessup, Brosnihan, Gallagher et al., 2008, Nehme, Zouein, Zayeri et al., 2019, Abadir, Walston and Carey, 2012, Kumar, Singh and Baker, 2008, Sherrod, Liu, Zhang et al., 2005). The presence of RAS proteins in tissue suggest that they are either locally synthesized and processed or represent precursors that are transported from the circulation and then processed locally (Ahmad and Ferrario, 2018, Ferrario, Ahmad, Varagic et al., 2016, Pendergrass, Averill, Ferrario et al., 2006, Whaley-Connell, Habibi, Nistala et al., 2012). Further, the processing mechanisms of the tissue RAS may differ from the circulating RAS and from one tissue type to another. For example, angiotensin II (Ang II) in the blood and the lungs is primarily generated by angiotensin converting enzyme (ACE) from angiotensin I (Ang I), whereas in tissues such as the bone marrow and the heart, chymase is the main Ang II-forming enzyme (Ahmad and Ferrario, 2018, Ferrario et al., 2016, Ahmad, Simmons, Varagic et al., 2011, Ahmad, Varagic, Groban et al., 2014, Ahmad, Varagic, VonCannon et al., 2016, Ahmad, Wei, Tallaj et al., 2013, Yamashita, Ahmad, Wright et al., 2020). The discovery of chymase as an Ang II generating enzyme originated in studies performed at the Cleveland Clinic by Bumpus and colleagues (Hirakata, Fouad-Tarazi, Bumpus et al., 1990, Kinoshita, Urata, Bumpus et al., 1991) three decades ago. Identification of angiotensin-(1-7) as a component of the RAS and the later demonstration of angiotensin converting enzyme 2 (ACE2) and the mas receptor (Mas-R) as constituents of the ACE2/Ang-(1-7)/Mas-R axis established the basis for a more insightful understanding of the system in the control of cell function and homeostasis. The current acceptance of the RAS as comprised by two intertwined biochemical arms with opposing functions [ACE/Ang II/AT_1-R and ACE2/Ang-(1-7)/Mas-R axis], provides a more complete vision of how homeostasis is regulated and how an unbalance in the expression or activity of the opposing arms of the RAS can associate with or cause tissue remodeling, endothelial dysfunction, and cardiac/vascular fibrosis, as well as alter normal cell biology with attendant unregulated control of cell growth and altered immunity (McMaster, Kirabo, Madhur et al., 2015, Mikolajczyk and Guzik, 2019).

The main goal of this review is to highlight the importance of alternate non-canonical pathways in which intermediate substrates representing peptides with amino acid sequences shorter than angiotensinogen (AGT) constitute an alternate substrate for the generation of the biologically active peptides Ang II and Ang-(1-7). These alternate angiotensin substrates are -the *dodecapeptide* angiotensin-(1-12) [Ang-(1-12)] and *ikosi pendi* peptide angiotensin-(1-25) [Ang-(1-25)]. While both polypeptides were identified by Japanese researchers in Miyazaki, Japan (Nagata, Hatakeyama, Asami et al., 2013, Nagata, Kato, Sasaki et al., 2006), the bulk of the evidence for a biological role as a source of Ang II production is on Ang-(1-12) as no further data for Ang-(1-25) has been published since the original publication (Nagata et al., 2013). We also discuss the beneficial role of chymase

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inhibition as a novel therapy in the treatment of progressive heart and kidney diseases, given chymase importance as an Ang-(1-12) degrading enzyme (Ahmad and Ferrario, 2018, Ansary, Urushihara, Fujisawa et al., 2018, Devarajan, Yahiro, Uehara et al., 2015, Duengen, Kim, Zahger et al., 2020, Dungen, Kober, Nodari et al., 2019, Kanefendt, Thuss, Becka et al., 2019). While the mechanisms that underlie the pathological effects of chymase at the cellular level are not yet well defined, new studies yield support to the use of novel chymase inhibitors in the management of human left ventricular dysfunction and heart failure (Duengen et al., 2020, Dungen et al., 2019, Kanefendt et al., 2019).

Ang-(1-12) and Chymase Role in RAS

The intracellular presence of the AGT protein along with its' metabolic products [Ang I, Ang II and Ang-(1-7)] are documented, even though more work needs to done in terms of understanding their intracellular compartmentalization and the specific conditions for their expression in the cell nuclei and cytosolic organelles (Abadir et al., 2012, Kumar et al., 2008,Barlucchi, Leri, Dostal et al., 2001, Gwathmey, Alzayadneh, Pendergrass et al., 2012, Sadoshima, Xu, Slayter et al., 1993, Singh, Le, Bhat et al., 2007).

Ang-(1-12) (aka proangiotensin 12) was first identified by Nagata et al. (Nagata et al., 2006) in 2006 from the blood and tissues of a japanese strain of Wistar rats. In this first study Nagata and co-workers (Nagata et al., 2006) demonstrated the ability of Ang-(1-12) to generate Ang II via angiotensin converting enzyme. In the pursuit of its potential role as an Ang II substrate, a series of studies from our laboratory showed the presence of immunoreactive (ir-) Ang-(1-12) products in the left ventricle and renal tubules of spontaneous hypertensive rats (SHR) (Jessup, Trask, Chappell et al., 2008) and rat cardio myocytes (isolated from 1-3 days old neonatal pups and adult hearts) (Ahmad et al., 2011, Ahmad, Varagic, Westwood et al., 2011). The potential contribution of Ang-(1-12) to cardiovascular regulation as an angiotensin peptide generating substrate was strengthened by additional studies showing that plasma membranes isolated from human normal left ventricular myocytes metabolized Ang-(1-12) into Ang II by chymase (Ahmad et al., 2013). Additional evidence was obtained from human biopsies of right and left atrial appendages of patients undergoing cardiac surgery for the treatment of resistant atrial fibrillation or left heart myocardial or valve disease (Ahmad et al., 2011, Wang, Varagic, Nagata et al., 2020, Wang, Varagic, Nagata et al., 2020). These studies showed a positive association among left atrial Ang-(1-12) expression, chymase gene transcripts, and chymase enzymatic activity levels in patients with enlarged left atria due to left heart disease (Wang et al., 2020a, Wang et al., 2020b). The increased activity of the Ang-(1-12)/chymase axis in these patients is in keeping with parallel demonstrations of a critical role of chymase in left atrial enlargement during volume overload (Dell'Italia, Collawn and Ferrario, 2018, Dell'Italia, Meng, Balcells et al., 1995, Powell, Wei, Fu et al., 2019) and in the evolution of primary mitral regurgitation (Butts, Ahmed, Bajaj et al., 2020).

It is generally accepted that hypertension, diabetes, aging, and oxidative stress stimulate the activity of the circulating and tissue-borne RAS (Chen, Juan and Chou, 2018, Conti, Cassis and Benigni, 2012, Ferrario, 2010, Ferrario, Ahmad, Joyner et al., 2010, Groban, Pailes, Bennett et al., 2006, Luo, Wang, Chen et al., 2015, Singh, Le, Khode et al., 2008). In

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keeping with these findings, intracellular levels of endogenous Ang-(1-12) are higher in neonatal myocytes isolated from 1-3 days-old pups of SHR compared to normotensive Wistar-Kyoto rats (WKY) (Ahmad et al., 2011). In addition, intact Ang-(1-12) was incorporated within cultured neonatal myocytes in a time-dependent fashion in both WKY and SHR. Importantly, the rate of Ang-(1-12) uptake was significantly higher in SHR as compared to WKY myocytes at all-time points (Ahmad et al., 2011).

Figure 1 illustrates the metabolic pathways leading to Ang-(1-12) generation and processing. While metabolism studies demonstrate the ability of angiotensin converting enzyme (ACE) to hydrolyze Ang-(1-12) into Ang I, this enzymatic pathway seems to be primarily accounting for Ang-(1-12) metabolism in the circulation during exposure to the rich ACE contained within the surface area of the vascular endothelium (Moniwa, Varagic, Simington et al., 2013). On the other hand, studies of Ang-(1-12) metabolism in tissues such as the heart and the kidneys point toward chymase as the critical enzyme metabolizing Ang-(1-12) directly into Ang II. Chymase participation in the metabolism of the Ang-(1-12) substrate was first identified in heart tissue lysate and atrial cardiomyocytes (Ahmad et al., 2011, Ahmad et al., 2016). In human atrial tissue, chymase affinity for Ang-(1-12) is 25-fold higher than for ACE (Wang et al., 2020a, Wang et al., 2020b). Ang-(1-12) preference for chymase has been further confirmed in rat bone marrow. In this tissue, chymase-mediated Ang II formation from Ang-(1-12) substrate was approximately 1,000-fold higher than that of ACE (Yamashita et al., 2020). These findings further indicate that the RAS processing enzymes are regulated differently at the cellular level. Chymase expression in tissues and its' deleterious effect in organ damage has been the topic of a recent review (Dell'Italia et al., 2018).

Chymase participation as an Ang II forming enzyme originates in studies performed at the Cleveland Clinic thirty years ago. In pursuing the observation that Ang I exerted significant cardiac inotropism in the presence of captopril (Hirakata et al., 1990), chymase was identified as an Ang II forming enzyme from Ang I by Urata et al. (Urata, Kinoshita, Misono et al., 1990, Urata, Kinoshita, Perez et al., 1991, Urata, Nishimura and Ganten, 1995). Additional novel contributions to chymase role in cardiovascular disease were done by Husain et al. (Husain, 1993, Ju, Gros, You et al., 2001, Murakami, Karnik and Husain, 1995, Wasse, Naqvi and Husain, 2012) and Dell'Italia and colleagues (Dell'Italia et al., 2018, Butts et al., 2020, Butts, Goeddel, George et al., 2017, Dell'Italia, Meng, Balcells et al., 1997, Pat, Chen, Killingsworth et al., 2010, Wei, Lucchesi, Tallaj et al., 2003).

The rich literature concerning chymase participation as an Ang II-forming enzyme, as reviewed recently (Dell'Italia et al., 2018), remains relegated as scientists and clinicians continue to ignore accumulating evidence of a high ***residual risk*** of cardiovascular events in patients medicated with ACE inhibitors (Ferrario et al., 2016, Ferrario and Mullick, 2017, Reyes, Cheng, Roberts et al., 2019, Reyes, Varagic, Ahmad et al., 2017). Limited acceptance of a critical contribution of chymase to human cardiovascular pathology is partly influenced by the existence of multiple isoforms expressed differently in rodents and humans. Of the five more prominent chymases found in rodents, mast cell protease 5 (MCP-5) is the most structurally and phylogenetically related to the human chymase encoded by the CMA1 gene (Rao and Hoidal, 2012).

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The human chymase gene (CMA1) has a significant association to immunity. A recent study showed significantly higher expression of CMA1 gene in gastric cancer tissues compared to adjacent normal tissues (Shi, Ye, Mao et al., 2020). The expression level of CMA1 (a key gene) in gastric cancer correlated with the levels of infiltrated CD^{4+}, CD^{8+}, neutrophils, macrophages, and dendritic cells (Shi et al., 2020). Past studies from Ferrario's laboratory implicated the existence of an immunological imbalance during the development of experimental renal hypertension as revealed by biphasic changes in the thymus weight (Chatelain and Ferrario, 1978) and a reduced thymus T cell reactivity (Chatelain, Vessey and Ferrario, 1980). Since T lymphocytes are important regulators of immunological homeostasis, this reduction in T-cells suggested the existence of an immunological imbalance accompanying the development of experimental renal hypertension. The thymus and the bone marrow are key players in immunity in part explained by the fact that T cells migrate to the thymus to undergo further growth and differentiation (2009). Consequently the first demonstration of the existence of the genes and proteins of the RAS in the bone marrow, including evidence of *de novo* synthesis of Ang II by marrow stromal cells (MSC) (Strawn and Ferrario, 2008, Strawn, Richmond, Ann Tallant et al., 2004), provided initial clues as to the role of altered immunity in the pathogenesis of human hypertension. Since Ang II is expressed in the bone marrow where it functions as an autocrine-paracrine modulator of hematopoiesis, we further explored whether Ang-(1-12) and chymase may be present. This new study revealed the abundant presence of Ang-(1-12) in the bone marrow of Sprague Dawley rats; moreover, we found that chymase-mediated Ang II-formation from Ang-(1-12) was approximately 1,000-fold higher than ACE (Yamashita et al., 2020). These data are consistent with a hereto unknown role of the Ang-(1-12)/chymase axis in the modulation of hematopoiesis and inflammatory mechanisms associated with the pathogenesis of hypertension. In keeping with this interpretation, we now find a significant expression of Ang-(1-12) in the rat's thymus (Figure 2).

Ang-(1-12) and Cellular Function

As of now, the two primary biologically active RAS components [Ang II and Ang-(1-7)] have been widely recognized for their direct cellular interactions and functionality. The most widely appreciated pathological function of the Ang II peptide is through its membrane receptor [Ang II type 1 receptor, AT_1R] signaling pathways where it modulates the structural characteristic of the cells in various diseases (Mehta and Griendling, 2007, Wolf and Wenzel, 2004). Our recent compelling studies show that Ang-(1-12) functions as a tissue non-renin dependent alternate precursor for direct Ang II generation by chymase in the rodent and human heart (Ahmad et al., 2013, Ferrario, Varagic, Habibi et al., 2009, Trask, Jessup, Chappell et al., 2008). We examined that *in vivo* Ang-(1-12) induced alterations in global cardiac function in adult normal Sprague Dawley rats (Li, Zhang, Cheng et al., 2018), WKY (De Mello, Dell'Itallia, Varagic et al., 2016), transgenic hypertensive rats expressing the human AGT [TGR(hAGT)L1623] (Reyes et al., 2019), and SD rats with isoproterenol-induced heart failure (HF) (Li, Zhang, Zhang et al., 2020). In all cases, Ang-(1-12) induces positive inotropic responses that are the result of intracellular Ca^{2+} mobilization (Reyes et al., 2019) and activation of K+ currents (De Mello et al., 2016). Ang-(1-12) contractile responses are reduced in rats with isoproterenol-induced HF (Li et al., 2020) and in the

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hypertensive myocytes of TGR(hAGT)L1623 rats (Reyes et al., 2019). Ang-(1-12) inotropic responses in isolated cardiac myocytes are significantly inhibited in the presence of a chymase inhibitor (chymostatin). These findings suggest that the Ang-(1-12) responses are mediated by intracellular processing of the substrate by chymase, - directly generating Ang II from the Ang-(1-12) substrate.

Therapeutic Aspect of Intracellular Cardiac Chymase/ACE Inhibition

Cardiovascular diseases (CVDs) are the number one cause of death (31%) globally. Challenges remain in designing effective therapeutic agents to block intracellular sites of Ang II generation. Previous studies from Singh et al. (Singh et al., 2008) showed that neonatal rat ventricular myocytes synthesize and retain Ang II intracellularly, and that Ang II is redistributed to the nucleus under high-glucose conditions. Further, these authors noted that cardiac myocytes grown in a high-glucose environment increase intracellular concentrations of AGT and chymase. Markedly increased chymase expression in vascular smooth muscle cells in human diabetic nephropathy, and hypertensive nephropathy has been reported (Cristovam, Carmona, Arnoni et al., 2012, Huang, Chen, Truong et al., 2003). A major role of ACE-independent formation of intrarenal Ang II in diabetes (Singh et al., 2007), and the involvement of renal mast cell chymase activity has been documented in patients with autosomal dominant polycystic kidney disease (McPherson, Luo, Brown et al., 2004). These studies suggest that cellular RAS physiology is changed under high-glucose conditions, a finding that agrees with our studies in which chymase (not ACE) had a significant role in Ang-(1-12) processing to generate Ang II in human and rat heart tissues.

ACE inhibitors and AT_1-R blockers are established as primary medications in the treatment of patients with hypertension and CVDs. While large well-conducted clinical trials demonstrate the beneficial effects of ACE inhibitors and ARBs in terms of blood pressure control and amelioration of target organ damage (Dusing, 2016), a more critical appraisal of their therapeutic efficacy in terms of reducing clinical events reveals an overall risk reduction of no more than 30% (Ferrario et al., 2016, Reyes et al., 2017, Ferrario, Ahmad, Nagata et al., 2014). Meta-analysis data from large clinical trials employing ACE inhibitors show a relatively small risk reduction of clinical cardiovascular endpoints (Reyes et al., 2017). In a critical reappraisal of blood pressure lowering trials in hypertension, Zanchetti *et al.*, (Zanchetti, Thomopoulos and Parati, 2015), reported an absolute risk reduction of 18% across all trials leaving a residual cardiovascular risk of 82%. Although ACE inhibitors and ARBs may effectively control blood pressure, the residual risk for cardiovascular events remains high. The presence of such a residual risk for cardiovascular events in the face of satisfactory blood pressure control may relate to the inability of these medications to reach intracellular sites at which Ang II exerts pathological actions (Kumar et al., 2008, Ferrario et al., 2016, Ferrario and Mullick, 2017). This hypothesis is supported by the failure of ACE inhibitors and/or ARBs to reduce the tissue expression of Ang II as demonstrated in the heart of normotensive (Ferrario, Jessup, Chappell et al., 2005) and hypertensive rat models (Jessup et al., 2008, Ferrario, VonCannon, Ahmad et al., 2019, Ferrario, VonCannon, Jiao et al., 2016, Jessup, Gallagher, Averill et al., 2006, Varagic, Ahmad, VonCannon et al., 2013). In keeping with these findings, intracrine effects of Ang II on cardiac myocyte growth and hypertrophy were not inhibited by the AT_1-R antagonist, losartan (Baker and Kumar, 2006).

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Further, these authors demonstrated that the intracellular effects of Ang II in isolated cultured myocytes is not inhibited by blocking the cell surface AT_1-R. These data indicate the independence of the intracrine RAS from the external environment (Baker and Kumar, 2006, De Mello, 1998).

Chymase inhibitors have been shown to protect diabetic rats from renal lesions (Maeda, Inoguchi, Takei et al., 2010, Zhang, Huang, Bai et al., 2016), cardiac dysfunction (Pat et al., 2010), and cardiac arrhythmias (Jin, Takai, Sakaguchi et al., 2004, Tsai, Lai, Hwang et al., 2008, Yahiro, Miura, Imaizumi et al., 2013). In mice, an orally active chymase inhibitor (TEI-F00806) showed antihypertensive effects that were associated with reduced renal AGT and Ang II content as well as chymase gene transcripts (Ansary et al., 2018). In ovariectomized, middle-aged Brown-Norway X Fischer344 rats, 4 weeks of treatment with the mast cell stabilizer cromolyn sulfate improved diastolic function and mitigated the adverse effects of estrogen loss on cardiac interstitial remodeling; effects associated with a reduction in cardiac Ang II immunoreactivity and a strong propensity for lessening of cardiac chymase activity (Wang, da Silva, Alencar et al., 2016). A recently completed safety and tolerability trial on adverse cardiac remodeling after acute ST-segment-elevation myocardial infarction (STEMI) with the orally active chymase inhibitor fulacimstat did not demonstrated superiority over standard care even though the medication was well tolerated, and devoid of negative effects on blood pressure and heart rate (Duengen et al., 2020, Dungen et al., 2019, Kanefendt et al., 2019).

Summary

Exploration of alternate renin-independent mechanisms for Ang II production are shedding a more precise view of the biochemical physiology of the RAS and its role in pathology. Ang-(1-12)'s function as a source for Ang II production in cardiovascular tissues may be more relevant than currently accepted. Buttressing this possibility, Ang-(1-12) role as a biomarker of worsening outcomes of the Acute Respiratory Distress Syndrome (ARDS) has now been revealed in a recently published study by Reddy et al. (Reddy, Asante, Liu et al., 2019). This study employed a liquid chromatography-mass spectrometry-based metabolomics assay to determine how plasma angiotensins correlated with clinical and pulmonary measures in survivors and non-survivors. Median plasma Ang-(1-12) concentrations and the Ang-(1-12)/Ang I ratio were markedly elevated in patients succumbing to the disease at 72 h post admission to the intensive care unit (Reddy et al., 2019).

A robust literature underscores the uniqueness of the AGT protein as the precursor substrate for the generation of angiotensin peptides in health and disease (Celerier, Cruz, Lamande et al., 2002, Clauser, Gaillard, Wei et al., 1989, Corvol and Jeunemaitre, 1997, Corvol, Persu, Gimenez-Roqueplo et al., 1999, Jeunemaitre, Charru, Chatellier et al., 1993, Jeunemaitre, Gimenez-Roqueplo, Celerier et al., 1999). While the first 10 amino acid sequence of from the N-terminus of AGT is conserved across species, the same is not true beyond position 10 (leucine). In humans, the next four amino acids from the N-terminal of AGT are Val^{11}-Ile^{12}-His^{13}-Asn^{14} while the same sequence in the rat is Leu^{11}-Tyr^{12}-Tyr^{13}-Ser^{14}. These differences in the N-terminal sequence of AGT amino acids explains the selective catalytic

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activity of human renin for human AGT (Ferrario et al., 2016,Ahmad et al., 2014, Ferrario, 2010). Moreover, little is known about the biological activity of “extended forms of Ang I”. Extended forms of Ang I that are immunologically and pharmacologically comparable to [Ile^5]-Ang I, and with molecular weights ranging between 1,300 and 2,200 daltons were identified in canine cerebrospinal fluid (Husain, Bumpus, Smeby et al., 1983). The function of the remaining 98% of the AGT protein [des-(Ang I)-AGT] remains to be fully investigated. Apparent independent functions not associated with Ang I activity and acting as an anti-angiogenic factor have been reported (Celerier et al., 2002, Corvol, Lamande, Cruz et al., 2003) while Lu and colleagues (Lu, Wu, Howatt et al., 2016, Tao, Rong, Lu et al., 2019) have linked des-(Ang I)-AGT to abnormalities in carbohydrate and lipid metabolism in mice. While research in Ang-(1-12) (Ferrario et al., 2016, Ferrario, 2016) and Ang-(1-25) (Nagata et al., 2013) has partially illuminated this issue much remains to be clarified. New research into the clinical significance of the Ang-(1-12)/chymase axis is of fundamental importance given the suggestion that inhibition of hepatic AGT using antisense oligonucleotides (Ferrario and Mullick, 2017, Mullick, Yeh, Graham et al., 2017, Ravichandran, Ozkok, Wang et al., 2015, Saigusa, Dang, Mullick et al., 2016) or small interfering RNAs (siRNAs) (Uijl, Mirabito Colafella, Sun et al., 2019) may constitute a novel approach to treat hypertension. At the 2020 virtual scientific sessions of the American Heart Association, Huang et al. (Huang, Taubel, Fiore et al., 2020) summarized in a poster the outcome of suppressing hepatic AGT synthesis with a subcutaneous investigational RNAi (ALN-AGT01) on the blood pressure in hypertensive patients. The data showed that ALN-AGT01 was effective in suppressing plasma AGT and dose-related decreases in blood pressure in the absence of hypotension and side-effects over an 8-week treatment period. However, the long-term consequences of suppressing at least 96% of the hepatic AGT to achieve a reduction in plasma Ang II and blood pressure remains a concern.

Uncovering the function of the Ang-(1-12) strengthens the urgency to explore the use of chymase inhibitors in cardiovascular pathology as exemplified by recent published results obtained in normal volunteers and patients post-myocardial infarction (Duengen et al., 2020, Kanefendt et al., 2019, Okamura, Okuda, Shirai et al., 2019). A more definitive characterization of the enzymatic pathway through which Ang-(1-12) is cleaved from AGT may project this alternate peptide as a more precise target to suppress Ang II pathological actions.

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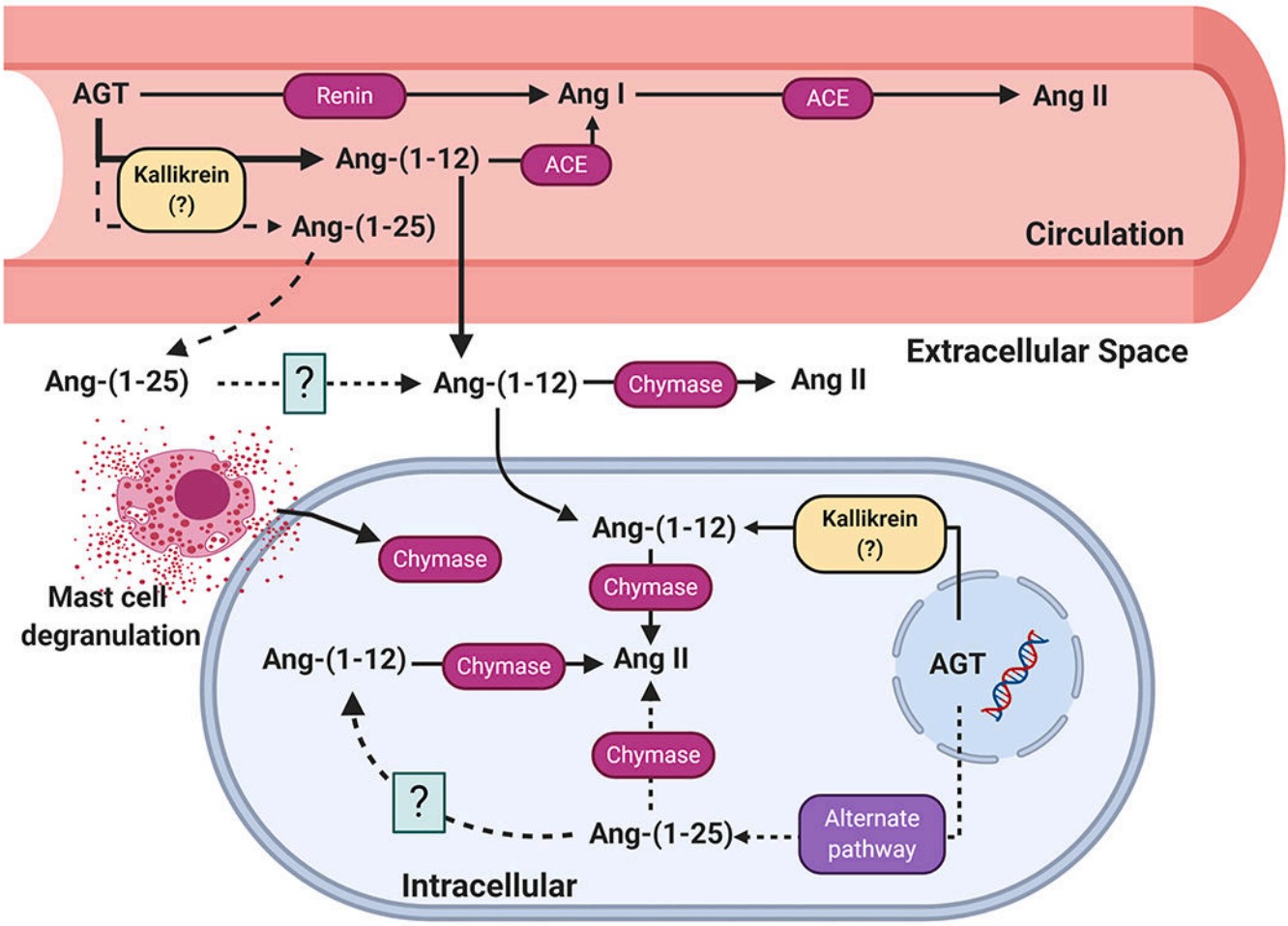

Figure 1.

Present view of the biochemical pathways involving the metabolism of angiotensin-(1-12) and angiotensin-(1-25) in the generation of angiotensins within the blood and tissues. Abbreviations as defined in text.

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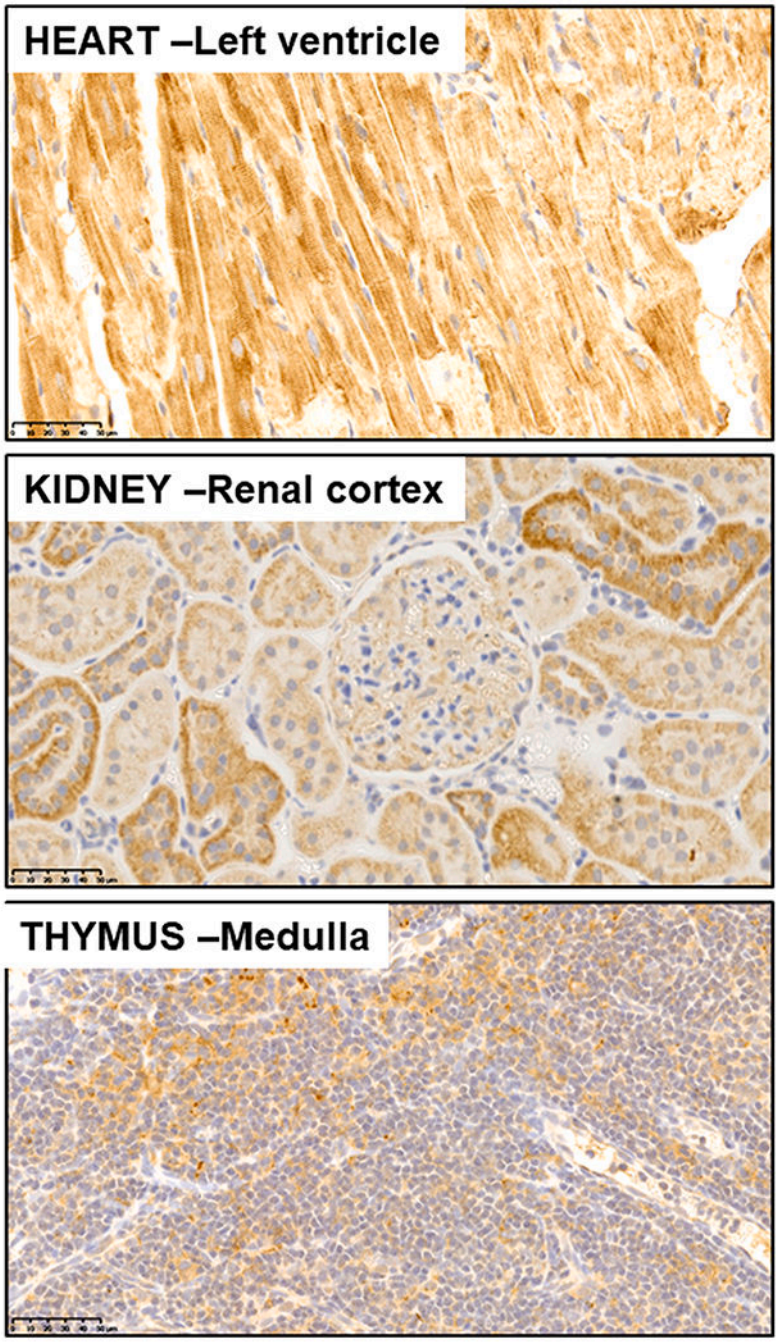

Figure 2.

Histological composite of immunoreactive expression of angiotensin-(1-12) in cardiac, renal, and thymus from a transgenic rat expressing the human angiotensinogen gene (Ferrario et al., 2019, Ferrario et al., 2016). As documented elsewhere, Ang-(1-12) localizes within cardiac myocytes, proximal and distal renal tubules, and shows a preferential presence in epithelial cells within the thymic medulla. The Ang-(1-12) staining is achieved

with a highly specific monoclonal antibody directed against the human Ang-(1-12) amino acid sequence.

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