Brief Review

Angiotensin-(1–7)

Robson Augusto Santos

Online Data Supplement

In the last decade, a substantial change in our understanding of the renin–angiotensin system (RAS) occurred. It is now clear that the circulating and tissue RAS are far more complex than previously anticipated. The modern concept of the RAS includes, in addition to the classical components (renin, angiotensin [Ang]-converting enzyme [ACE], Ang II, Ang III, and Ang type 1 and type 2 receptors [AT1R and AT2R]), novel enzymes, peptides, and receptors (ACE2, Ang-(1–7), (pro)renin receptor, and Mas). More recently, novel putative components of the RAS (Ang A, alamandine, and the Mas-related G-protein–coupled receptor D) were identified. These new discoveries bring into perspective new possibilities of interaction among RAS components. Figure 1 shows a simplified updated view of the RAS.

The demonstration that Ang-(1–7) is a key component of the RAS represented one of the most significant conceptual changes of this important hormonal system. This review will focus on the cardiovascular actions of Ang-(1–7) and the potential of Ang-(1–7) and other Mas agonists as cardiometabolic therapeutic agents. Figure 2 shows most of known cardiovascular actions of Ang-(1–7). It should be pointed out that the actions of Ang-(1–7) are not restricted to the cardiovascular system. For example, Ang-(1–7) also impacts the renal system, which may play a role in cardiovascular diseases, such as hypertension. Because of space limitation, only a partial list of references was included in the text. An expanded reference list is available in the online-only Data Supplement.

Cardiovascular Actions of Ang-(1–7)

Heart

There is a vast array of literature concerning the effects of Ang-(1–7) in the heart. Averill et al were the first to report the presence of Ang-(1–7) immunoreactivity within myocytes in the rat heart. This was in line with the presence of Ang-(1–7) immunoreactivity in blood collected from the canine coronary sinus. More recently, Ang-(1–7) and Mas were identified in the sinoatrial node, providing the morphological basis for the Ang-(1–7) antiarrhythmic effect.

The presence of ACE2 in cardiomyocytes further supports a local formation of Ang-(1–7) in the heart of different species. It should be pointed out that other enzymes capable of directly or indirectly forming Ang-(1–7) are also present in the heart, including prolyl-oligopeptidase and cathepsin A.

Coronary Vessels

Ang-(1–7) produces vasorelaxation in the coronary vessels of dogs and pigs. In rodents, the peptide was, in general, without effect or produced vasoconstriction. However, these observations were made using relatively high concentrations of Ang-(1–7), in the nanomolar to micromolar range. Recently, using picomolar concentrations of Ang-(1–7), Souza et al were able to unveil a significant vasodilator effect of Ang-(1–7) in isolated rat hearts. This effect was offset in hearts taken from aorto-coarcted rats. Intriguingly, the blunted Ang-(1–7)–induced vasodilation in hypertensive animals was restored by acute or chronic AT-A1 blockade with losartan. These observations are in keeping with the previously described interaction of AT-R with Mas, which still needs to be addressed in more detail.

Cardiomyocytes

In cardiomyocytes, acute exposure to Ang-(1–7) has no demonstrable effect on Ca2+ transient but promotes nitric oxide (NO) release by activating endothelial NO synthase (eNOS) and neuronal NO synthase. Whereas, chronic exposure to Ang-(1–7) or genetic deletion of Mas produces significant effects on Ca2+–handling proteins. Transgenic rats harboring an Ang-(1–7)–producing fusion protein in the heart show an increased Ca2+ transient amplitude, faster Ca2+ uptake, and increased expression of SERCA2. Cardiomyocytes from Mas-KO (knockout) mice have a smaller peak Ca2+ transient and slower Ca2+ uptake, probably because of the decreased expression of SERCA2. These changes were translated into decreased heart function in Mas-KO mice. The changes in calcium-handling proteins were paralleled by changes in the NO production machinery. Cardiomyocytes from Mas-KO mice have normal eNOS protein levels, but a 70% increase in...
in caveolin 3 expression and a decrease in heat shock protein 90. These 2 alterations may lead to a decrease in eNOS activity because caveolin 3 prevents calmodulin interaction with NOS, and heat shock protein 90 acts as a scaffold protein to recruit protein kinase B (AKT) to the eNOS complex.

**Ang-(1–7) and Cardioprotection**

Most of the data related to Ang-(1–7) or other Mas agonists in the heart deal with its cardioprotective effects.

The first description of a cardioprotective effect of Ang-(1–7) was made by Ferreira et al. A low concentration (220 pmol/L) of Ang-(1–7) produced a significant reduction of ischemia/reperfusion-induced cardiac arrhythmias in isolated rat hearts. This was in contrast with the proarrhythmogenic effect of Ang-(1–7) at 10-fold higher concentrations. De Mello et al reported a biphasic effect of Ang-(1–7) on impulse propagation and cardiac arrhythmias: at 10 nmol/L, an antiarrhythmic effect was observed, whereas at a 10-fold higher concentration, Ang-(1–7) was proarrhythmic. In transgenic TG(A1-7)L-3292 rats with a 2.5-fold increase in circulating Ang-(1–7), reduced duration of reperfusion cardiac arrhythmias and an improved postischemic heart function were observed. The mechanism of the antiarrhythmic effect of Ang-(1–7) seems to involve the sodium pump.

In addition to influencing cardiac rhythm, Ang-(1–7) produces a significant antiremodeling effect in different models of cardiomyopathy. In TG(A1-7)L-3292 rats, a marked attenuation of isoproterenol-induced cardiac fibrosis was reported.

Later, many other studies described the antiremodeling effects of Ang-(1–7) and of other Mas agonists (AVE0991, CGEN-8565; see the online-only Data Supplement). These observations are in line with the deleterious cardiac effects of genetic ablation of Mas in mice. Interestingly, even acute blockade of Mas with A-779 has been reported to produce deterioration of heart function in isolated mouse hearts.

In contrast to the consistent antifibrotic effect of Ang-(1–7)/Mas, more variable results were obtained for cardiomyocyte hypertrophy, although in general an antihypertrophic effect is described. The prohypertrophic effect of isoproterenol was attenuated in TG(A1-7)L-3292 rats. Similarly, treatment with Ang-(1–7) attenuated Ang II–induced cardiac hypertrophy.

However, in the DOCA-salt model of hypertension, treatment with Ang-(1–7) attenuated cardiac fibrosis without interfering with blood pressure or cardiac hypertrophy. Whereas, induction of DOCA-salt hypertension in transgenic rats harboring an
Ang-(1–7)–producing fusion protein resulted in the attenuation of hypertension, myocardial fibrosis, and cardiac hypertrophy. An antihypertrophic effect of Ang-(1–7) was also observed in cultured cardiomyocytes treated with Ang II, vasopressin, and endothelin.

Contrasting with several reports showing a cardioprotective effect of Ang-(1–7), Velkoska et al reported a dramatic deleterious effect of Ang-(1–7) infusion in Sprague–Dawley rats after 5/6 nephrectomy. However, Li et al in the mouse and, more recently, Xu et al in the rat described opposite effects. In their studies, treatment with Ang-(1–7) prevented heart dysfunction and left ventricular remodeling. Therefore, additional studies are needed to clarify these conflicting data. It would be interesting, for example, to remove the interfering factors such as endothelin 1, which is increased in this model of nephropathy. Endothelin 1 decreases Mas expression, which could favor an action of Ang-(1–7) on AT1R receptors in this condition. Another contrasting report is the one by Zhang et al. These authors showed that the overexpression of human Mas in rat cardiomyocytes leads to hypertrophy. Despite the possibility that overexpressed receptors could be uncoupled from the usual signaling machinery activated by endogenous receptors, these data and others with Ang-(1–7) indicate that important differences in signaling may arise in conditions where Mas or Ang-(1–7) are increased above the supraphysiological concentrations.

Blood Vessels

Ang-(1–7) is formed in the endothelial layer of human blood vessels, which also express Mas. The formation of Ang-(1–7) in the vascular wall has also been described in other species. In addition, Mas is also expressed in the endothelium and vascular smooth muscle cells of different species.

Despite forming Ang-(1–7), the blood vessels are one of the main sites for its effects. Ang-(1–7) produces vasodilation in aortic rings and in several vascular territories. In normotensive rodents, the effect of Ang-(1–7) in these territories leads to a decrease in total peripheral resistance with a consequent increase in cardiac output. The hemodynamic impacts of these alterations on blood pressure are essentially equivalent, leading to no net change in blood pressure.

Studies performed in experimental models of permanent gain or loss of function also indicate that Ang-(1–7) is capable of chronically influencing systemic and local hemodynamics. It has been reported that Mas-deficient mice show an important increase in the vascular resistance of many territories such as kidney, lung, adrenal gland, mesentery, spleen, and brown fat tissue. A parallel increase in total peripheral resistance and decreased cardiac index was also observed. In contrast, in transgenic rats with a lifetime slight increase in circulating TG(A1-7) L-3292, the opposite change was reported. These data suggest the existence of an Ang-(1–7)/Mas tonus in blood vessels with a previously unsuspected physiological relevance. However,
because these regional blood flow measurements were made under anesthesia, caution should be exercised in terms of transposing these findings to nonanesthetized animals.

One of the most prominent consequences of mas deletion in mice is endothelial dysfunction.56,57 In the FVB/N background, endothelial dysfunction is associated with an increase in blood pressure,56 whereas in C57BL/6 mice, no alteration of blood pressure was reported.61 The endothelial dysfunction associated with Mas deficiency in these 2 genetic backgrounds in mice is in keeping with the improvement of endothelial function produced by short-term Ang-(1–7) infusion in normotensive rats62 and with the Mas-mediated improvement of vascular function in many species and conditions.63–65 Furthermore, these observations agree with the worsening of 2 kidney–1 clip hypertension in Mas-KO mice.66

In addition to its effects on endothelial function and vascular tone, Ang-(1–7) has antiproliferative effects in vascular smooth muscle cells.58 A similar effect was described for AVE0991.66 This feature seems not to be restricted to vascular smooth muscle cells because Ang-(1–7) has well-documented antiproliferative effects in other cell types, including cardiac fibroblasts67 and tumor cells.68,69

In humans, the initial reports using indirect forearm blood flow measurements were somewhat controversial. In patients chronically treated with ACE inhibitors, a condition in which circulating levels of Ang-(1–7) are markedly increased,71 the infusion of Ang-(1–7) was without effect on forearm blood flow, whereas the infusion of bradykinin produced a pronounced vasodilation. This observation was interpreted as evidence for a lack of relevance of Ang-(1–7) to the hemodynamic effects of ACE inhibitors. However, in this particular condition (ACE inhibitor treatment), the use of an Ang-(1–7) antagonist rather than Ang-(1–7) would have been more appropriate to reach such conclusions. A negative result was also reported by Wilksdorf et al,72 who observed that Ang-(1–7) was without effect in the forearm blood flow of normotensive patients and did not alter vasodilation produced by bradykinin infusion. In contrast, Sassaki et al73 observed a dose-dependent vasodilation. In addition, a dose-dependent potentiation of bradykinin vasodilation by Ang-(1–7) was described by Ueda et al,74 who observed that Ang-(1–7) was without effect in the forearm blood flow of normotensive patients. Further evidence of the antiproliferative effects of Ang-(1–7) was described by Rocks et al75 using mammary arteries in vitro. Moreover, recently, van Twist et al76 observed a significant dose-dependent increase in blood flow to the kidney during intrarenal infusion of Ang-(1–7) in hypertensive patients. Interestingly, this effect was attenuated in patients on a low-salt diet, probably because of the fact that low-salt diet leads to an increase in circulating angiotensin peptides, including Ang-(1–7).77 A similar attenuation was described by Rocks et al75 in rats. Despite methodological differences, the contrasting results obtained in humans could be because of racial or vascular territory differences in the sensitivity to Ang-(1–7). Further studies are obviously needed to confirm in humans the potent vasodilator effect of Ang-(1–7) described in rodents.59,60

**Mechanism of the Vascular Effects of Ang-(1–7): Mas or Mess?**

We and others have provided evidence for a critical role of Mas in the vascular effects of Ang-(1–7).79–81 Sampaio et al were the first to show the presence of Mas in cultured human aortic endothelial cells.82 The stimulation of these cells or Mas-transfected Chinese hamster ovary cells with Ang-(1–7) promoted NO release involving Mas and the phosphoinositide 3-kinase/AKT pathway.83 In human aortic endothelial cells, Ang-(1–7) also attenuated the effects of Ang II on signaling linked to the MAPK pathway.82 The Mas antagonist A-799 blocked these effects. More recently, Verano-Braga et al,83 using a time-resolved phosphoproteomics approach, were able to uncover many other signaling components of the Ang-(1–7) effects in human aortic endothelial cells, including FOXO1, which is activated by Ang-(1–7) and has an important counter-regulatory relationship with AKT-mediated effects.84 The data obtained in human endothelial cells are consistent with the absence of the effects of Ang-(1–7) in aortic rings taken from Mas-KO mice.6,57,85 The vasodilator effect of Ang-(1–7) was also markedly attenuated in mesenteric arteries of Mas-KO mice.86 In line with these observations, the vasodilator effect of the Ang-(1–7) mimetic, AVE0991, was blunted in aortic rings taken from Mas-KO mice, whereas the effect of the AT2R agonist, CGP42112A, was fully preserved.85 An essential role of Ang-(1–7)/Mas in the endothelium is suggested by the pronounced endothelium dysfunction present in C57BL/6 and FVB/N Mas-deficient mice.56,61 Accordingly, acute infusion of Ang-(1–7) in rats improved endothelial function.87

**Is AT2R Involved in Ang-(1–7)–Induced Vasorelaxation?**

In contrast with the body of evidence favoring a critical role of Mas in Ang-(1–7) vascular effects, studies using mostly the putative AT2R antagonist, PD123319, suggested an important role of AT2R in the vascular effects of Ang-(1–7) in some conditions.68–70 However, we have recently reported that PD123319 can compete with the novel angiotensin peptide alamandine for binding to Mas-related G-protein–coupled receptor D and, more importantly, that PD123319 blocked the vasodilator effect of alamandine in aortic rings taken from AT2-KO mice.8 Therefore, the possibility that PD123319 is actually blocking alamandine formed from Ang-(1–7) when it seems to be blocking the direct effects of Ang-(1–7) should be considered. We have observed that Ang-(1–7) also produces vasorelaxation in aortic rings and microvessels of AT2-KO mice (Caldeira and Santos, unpublished results). Likewise, it has been recently shown that the hypotensive effect of Ang-(1–7) in anesthetized mice is preserved in mice that are deficient in 3 Ang II receptors (AT1A, AT1B, AT2).72 These observations clearly disregard AT2R as a critical component of the vasodilator effect of Ang-(1–7). In keeping with this finding, PD123319 cannot block other vascular or nonvascular effects of Ang-(1–7).56,62,63,64 Whereas, the possibility of physical or functional interaction of Mas with AT2R should be seriously considered.63,86,89,95,96

In addition to the still unclear involvement of AT2R in Mas-mediated effects of Ang-(1–7), a possible crosstalk of bradykinin B1 receptors with Mas and AT2R has been suggested.23,88,97
A permissive role of bradykinin B₂ receptors, possibly involving heat shock protein 90 and other components of the NO-releasing machinery in the Mas-mediated and AT₂R-mediated effects, awaits elucidation. There are only sparse reports implicating AT₂R in the vascular effects produced by Ang-(1–7).²⁸

Taken together, the available data indicate that most if not all of the actions of Ang-(1–7) are mediated through Mas. The formation of novel peptide alamandine from Ang-(1–7) may explain, at least in part, the reports showing the absence of effects of A-779 on Ang-(1–7) actions.⁹⁹–¹⁰¹ because alamandine acts by a Mas-independent mechanism. The formation of alamandine can also explain the blockade of Ang-(1–7) effects by the analogue D-Pro7-Ang-(1–7) but not by A-779, because this antagonist blocks alamandine.¹⁰⁰¹⁰¹ Finally, the formation of alamandine may explain the blockade of some Ang-(1–7) effects by PD123319 due to Mas-related G-protein–coupled receptor D. These possibilities await confirmation. Nevertheless, the contribution of AT₂R and BK receptors for the vascular effects of Ang-(1–7) cannot be disregarded.

Central Cardiovascular Effects

It is well known that centrally Ang-(1–7) produces several cardiovascular-related and nonrelated effects.⁹²–¹⁰²–¹²² As observed for many centrally active substances, the cardiovascular effects produced by the central administration of Ang-(1–7) are complex, site-specific, and dependent on the physiological condition. In contrast with the many systemic opposing actions of Ang-(1–7) and Ang II, both peptides can produce similar effects in some brain regions.⁹²,¹⁰²,¹⁰⁴ However, the effector mechanisms are not always the same.¹¹⁹ For instance, in the rostral ventrolateral medulla (RVLM), microinjection of Ang-(1–7) and Ang II produced a similar pressor effect.⁹²,¹⁰⁴,¹¹⁹ The blockade of Ang-(1–7) or Ang II at the RVLM decreased blood pressure in hypertensive rats,¹²³ an effect that has been reassessed recently.¹²⁰,¹²⁴,¹²⁵ However, the pressor effects of Ang II and Ang-(1–7) at the RVLM seem to be mediated by different peripheral mechanisms. Although the Ang II pressor effect includes basically an increase of sympathetic activity,¹⁰⁵ the one produced by Ang-(1–7) includes vasopressin release and decrease of a vasodilator parasympathetic-related vascular tonus.¹¹⁹ Interestingly, at the RVLM, the Ang-(1–7) pressor effect increased after bleeding, whereas the Ang II effect remains essentially unaltered.¹⁰⁶ Similar differential mechanisms were reported for the hypotensive effect of Ang II and Ang-(1–7) activity at the caudal ventrolateral medulla.¹²¹ The hypotensive effect of Ang II at the caudal ventrolateral medulla involves a reduction of sympathetic activity, whereas the effect of Ang-(1–7) seems to also involve a nitrergic peripheral mechanism.¹⁰⁹

Using neurohypophyseal–hypothalamic explants, Schiavone et al.²⁶ described the first biological action of Ang-(1–7), the release of vasopressin. A few years later, Felix et al.¹²⁷ reported a neurostimulatory effect of Ang-(1–7) in paraventricular nucleus neurons. Subsequent studies over the past 20 years are in line with these initial findings (see the online-only Data Supplement). It is interesting that the mechanisms underlying the stimulatory effects of Ang II and Ang-(1–7) in the hypothalamus are also apparently distinct. It has been suggested that the effect of Ang II is linked to reactive oxygen species production. In the paraventricular nucleus, unlike many other brain regions in which NO release plays a major role,¹³¹,¹³⁶ Ang-(1–7) seems to exert its neuroexcitatory effects by a mechanism involving cyclic adenosine monophosphate/protein kinase A.¹³⁸ In contrast to its central sympathostimulatory effects at the paraventricular nucleus and RVLM, Ang-(1–7) has recently been reported to produce pronounced inhibition of β-adrenergic–mediated heart rate response to air jet stress or disinhibition of the dorsomedial hypothalamus.¹²¹ A decrease of renal nerve activity was also observed. This sympathoinhibitory action was observed after peripheral or central Ang-(1–7) administration.¹²¹

Remarkably, the nucleus tractus solitarius is one of the brain regions in which there is a clearcut difference between the cardiovascular effects of Ang II and Ang-(1–7). Although both peptides decrease blood pressure when microinjected in the femtomolar range in the nucleus tractus solitarius,¹⁰² in the baroreflex, the control of heart rate is opposite: Ang-(1–7) facilitates whereas Ang II decreases baroreflex sensitivity.¹⁰⁷,¹¹⁰,¹¹⁹ In keeping with these observations, intracerebroventricular (ICV) infusion of both peptides also produces opposite effects in the baroreflex.¹⁰³ Moreover, Mas-KO mice present decreased baroreflex sensitivity.¹¹⁴ Accordingly, it has been reported that in vivo expression of Ang-(1–7) lowers blood pressure and improves baroreflex function in TGR(mREN2)L-27 rats.¹¹⁷

In view of the many site-dependent cardiovascular effects of Ang-(1–7) in the central nervous system, one might ask what would be the net effect of an increased production of this heptapeptide in the brain. Acute ICV infusion of Ang-(1–7) in Wistar rats did not change blood pressure as well as water-drinking behavior.¹³⁰ This contrasts with the well-known pressor effect and induction of water and salt intake induced by Ang II.¹³¹ Whereas, ICV infusion of Ang-(1–7) in TGR(mREN2)L-27 or chronic ICV infusion of Ang-(1–7) in DOCA-salt hypertensive rats decreased blood pressure.¹¹¹,¹¹⁸ Similarly, the delivery of an Ang-(1–7)-producing fusion protein into the cisterna magna of TGR(mREN2)L-27 reduced blood pressure. Therefore, it seems that in the brain, despite several local similarities in the action of Ang II and Ang-(1–7), these 2 angiotensins exert opposite influences on blood pressure. Moreover, even when producing similar cardiovascular effects in a brain region, different signaling/effectector mechanisms are involved. What are the pathophysiological conditions or the afferent signals governing the differential expression of Ang II and Ang-(1–7) in different brain regions? These are pivotal questions that deserve future studies. In this regard, in the hippocampus, a novel pathway for the generation of Ang-(1–7) directly from Ang I and independent of ACE2 was recently described,¹²² opening new possibilities for site-specific regulation of angiotensin peptide processing. Interestingly, this possibility was also taken into consideration in the initial descriptions of Ang-(1–7) formation from radiolabeled Ang I in the brain stem.¹³² It is worth mentioning that, as discussed for blood vessels, there is evidence for the participation of AT₂R in some of the central effects of Ang-(1–7).¹³³ However, the same concerns pointed out for blood vessels should be taken into consideration when interpreting data obtained with the currently available AT₂R antagonists.
Ang-(1–7) and Other Mas Agonists in Cardiovascular Therapeutics: A Journey From Basics Physiology to Patients

As addressed above, a large body of evidence for vascular and cardioprotective roles for Ang-(1–7) was built in the past 2 decades. Similarly, although less complete, basic knowledge was also collected for the other available Mas agonists, AVE0991 and CGEN-8565.152,154–158 These observations lead to the quite unusual therapeutic strategy of stimulating, rather than blocking, a G protein–coupled receptor. The fact that transgenic rats and mice with lifelong increases in circulating or local Ang-(1–7) show clear signals of beneficial effects, resembling those observed with acute or short-term (weeks) administration of the peptide, indicates that desensitization or tachyphylaxis did not occur with chronic Mas stimulation. In addition to Mas stimulation, the use of putative ACE2 activators is a possibility being tested in experimental animals.139 Figure 3 shows the different tools available for exploring the therapeutic potentials of activating the ACE2/Ang-(1–7)/Mas axis. In addition to Mas, therapeutic strategies aimed at stimulating AT2R are also in progress.140–142

One of the approaches that have been well tested in animals is an inclusion compound, hydroxypropyl-β-cyclodextrin/Ang-(1–7). This patented compound protects Ang-(1–7) from inactivation by the digestive tract enzymes, which allows its oral administration.145 It should be emphasized that only Ang-(1–7) enters the blood stream in this case. The inclusion compound acts as a sustained-release system or more properly as a longlasting releasing system. Using this approach, many beneficial cardiovascular and metabolic effects of Ang-(1–7) were recently described, including antithrombogenesis,144,145 attenuation of cardiac remodeling induced by isoproterenol treatment,146 reduction of the lesion area and attenuation of acute and chronic postinfarction cardiac dysfunction,146,147 antihypertensive effect,148 and beneficial effects on erectile dysfunction,149 muscular dystrophy,150 and type II diabetes mellitus.151 In these preclinical studies, the beneficial effects observed were remarkable, considering that the peptide was given orally once a day in doses ranging from 10 to 50 μg/kg, equivalent to 11 to 55 nmol/kg per day. Ongoing phase I studies will provide data about the potential use of this hydroxypropyl-β-cyclodextrin/Ang-(1–7) inclusion compound for the treatment of human diseases.

In addition to the approach using cyclodextrins, the use of cyclic Ang-(1–7) is under preclinical testing.152,153 Cyclic Ang-(1–7) is more resistant than Ang-(1–7) to enzymatic hydrolysis. Interestingly, vasorelaxation produced by cyclic Ang-(1–7) in aortic rings from Sprague–Dawley rats is only partially blocked by the Mas antagonist A-779.153 Whereas, the Ang-(1–7) analogue D-Pro7-Ang-(1–7), an Ang-(1–7)/alamandine antagonist,6 completely blocked its effect. This pharmacological profile suggests that cyclic Ang-(1–7) could be a dual Mas/Mas-related G-protein–coupled receptor D agonist showing Ang-(1–7)/alamandine characteristics. This possibility awaits clarification.

An intravenous formulation of Ang-(1–7) has been tested in preeclamptic patients. After 48 hours of continuous Ang-(1–7) administration, a significant improvement in endothelial function was observed.154 Considering that endothelial dysfunction is the core of physiopathological alterations observed in preeclampsia, this finding opens the possibility for the use of Ang-(1–7) or other Mas agonists as a novel therapeutic tool for preeclamptic patients. However, additional studies are obviously needed to confirm this possibility.

Rodgers and diZerega and their coworkers155–158 have explored the use of Ang-(1–7) or Ang-(1–7) analogues for noncardiovascular indications, especially recovery from radiotherapy. The possibility of the use of Ang-(1–7) for the treatment of tumors is currently being tested.159

Concluding Remarks: Perspectives

Twenty-five years ago, the first articles describing the formation and actions of Ang-(1–7) were published. From the initial skepticism concerning its biological relevance, because it was considered only a degradation product of Ang I and Ang II,160,161 this peptide has achieved the status of a biologically active endproduct of the RAS, especially after the identification of ACE2 and its receptor Mas. More importantly, the possibility of using Ang-(1–7) or other Mas agonists as therapeutics agents is being more and more explored. This may represent an important paradigm shift in the method of interfering with the RAS activity for treating cardiovascular diseases: instead of blocking the hypertensive axis of the system, the possibility of stimulating the protective axis of the RAS seems to be an attractive therapeutic alternative. Ongoing clinical studies to be finished in the next few years will be important to confirm this possibility.

Acknowledgments

I am thankful to Professor Amy Milsted for kindly revising the article and to my Postdoc student Gisele Etelvino for the help in preparing the article.
Source of Funding

This work was supported by Conselho Nacional de Pesquisas (CNPq), Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

Disclosures

None.

References


Downloaded from http://hyper.ahajournals.org/ by guest on September 15, 2017


Angiotensin-(1-7) does not affect vasodilator or TPA responses to bradykinin in human forearm. Hypertension. 2001;37:1136–1140.


micro-injection of angiotensin-(1-7) on vasopressor and vasodepressor activity. 
mediated by angiotensin-(1-7) in the rostral ventrolateral medulla involves multiple peripheral mechanisms. 

Couto AS, Baltatu O, Santos RA, Ganten D, Bader M, Campagnole-Santos MJ. Hypotensive effects of 
angiotensin-(1-7) on rostral ventrolateral medulla in spontaneously hypertensive rats. 

Dobruch J, Pazwa P, Loš S, Kholis MC, Szczepańska-Sadowska E. Hypotensive function of the brain angiotensin-(1-7) receptor Mas-knockout mice. 

Feireira PM, Alzamora AC, Santos RA, Campagnole-Santos MJ. Hemodynamic effect produced by microinjection of angiotensins at the caudal ventrolateral medulla of spontaneously hypertensive rats. 

Dupont AG, Brouwers S. Brain angiotensin peptides regulate sympathetic tone and blood pressure. 

Hypertension. 2011;58:627–634.

Garcia-Espinosa MA, Shaltout HA, Cappell PE, Diz DI. In vivo expression of angiotensin-(1-7) lowers blood pressure and improves baroreflex function in transgenic (mRen2)272 rats. 

Guimaraes PS, Santiago NM, Xavier CH, Velloso EP, Fontes MA, Santos RA, Campagnole-Santos MJ. Chronic infusion of angiotensin-(1-7) into the lateral ventricle of the brain attenuates hypertension in DOCA-salt rats. 

Oliveira EC, Campagnole-Santos MJ, Santos RA. Thepressor effect of angiotensin-(1-7) on rostral ventrolateral medulla involves multiple peripheral mechanisms. 

Li P, Sun HJ, Cui BP, Zhou YB, Han Y. Angiotensin-(1-7) in the rostral ventrolateral medulla enhances cardiac sympathetic afferent and reflex synaptic activation in renovascular hypertensive rats. 


Schiaffone MT, Santos RA, Brosnihan KB, Khols MC, Ferrario CM. Release of vasopressin from the rat hypothalamo-neurohypophyseal system by angiotensin-(1-7) heptapeptide. 

Cardiovascular Actions of Angiotensin-(1–7)


Angiotensin-(1–7)
Robson Augusto Santos

Hypertension. 2014;63:1138-1147; originally published online March 24, 2014;
doi: 10.1161/HYPERTENSIONAHA.113.01274

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/63/6/1138

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2014/03/24/HYPERTENSIONAHA.113.01274.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/
ANGIOTENSIN-(1-7)

Online Supplement

Robson Augusto Souza Santos

Running Title: Cardiovascular actions of angiotensin-(1-7)

National Institute of Science and Technology in Nanobiopharmaceutics

Department of Physiology and Biophysics

Institute of Biological Sciences, Federal University of Minas Gerais

Belo Horizonte, Minas Gerais, Brazil, CEP:31270-910

Phone: 55-31-34092956

FAX : 55-31-34092924

Email: robsonsant@gmail.com
EXTENDED REFERENCES LIST


27. Canals M, Jenkins L, Kellett E, Milligan G. Up-regulation of the angiotensin ii type 1 receptor by the mas proto-oncogene is due to constitutive activation of gq/g11 by mas. *J Biol Chem.* 2006;281:16757-16767.


49. Santiago NM, Guimarães PS, Sirvente RA, Oliveira LA, Irigoyen MC, Santos RA, Campagnole-Santos MJ. Lifetime overproduction of circulating angiotensin-(1-7)


60. Cunha TM, Lima WG, Silva ME, Souza Santos RA, Campagnole-Santos MJ, Alzamora AC. The nonpeptide ang-(1-7) mimic ave 0991 attenuates cardiac remodeling and


68. Velkoska E, Dean RG, Griggs K, Burchill L, Burrell LM. Angiotensin-(1-7) infusion is associated with increased blood pressure and adverse cardiac remodelling in rats with subtotal nephrectomy. *Clin Sci (Lond).* 2011;120:335-345.


