Review Paper

Angiotensin 1-7~~,~~: A~~a~~ second window of protection in hypertensive patients

Abstract

The effects of the renin-angiotensin-aldosterone system on the human body are so diverse and our knowledge about them is ever growing. Angiotensin 1-7 has been proven to play protective roles in patients with cardiovascular disorders including but not limited to hypertension.

As is the case with Africa, ~~T~~the prevalence of hypertension in Sudan ~~as it is in Africa~~ is rising, and its complications could be delayed by pharmacologically manipulating the levels of renin-angiotensin system metabolites.

The aim of this review is to compare the advantageous and deleterious effects of Angiotensin 2 in contrast to those of Angiotensin 1-7 and to assert the well-established protective effects of Angiotensin 1-7 (systemically and locally) in hypertensive patients

Keywords: angiotensin 1-7, angiotensin 1, angiotensin II, angiotensin converting enzyme, and renin angiotensin system

Introduction

"The heart is the beginning of life, for it is by the heart the blood is moved, in which the source of all action is". Those were the words W. Harvey wrote in 1673. Corvisart in 1806 further elaborated that the cardiac muscle could change in structure due to disease. When he described

"two types of dilatation, active with thick walls and increased force of contraction, and passive with thinning of the walls and a decreased force of contraction. (1)

Cardiac enlargement is considered to be a very important coping mechanism as far as compensation goes in response to increased hemodynamic load. (2)

In Africa, where morbidity and mortality such as those attributed to cardiovascular diseases are increasing every year, the economic burden is self-evident. New areas of research with clinicians being more involved in areas with a genetic background such as Renin Angiotensin Aldosterone System (RAAS) promise novel approaches on both diagnostic and pharmacological levels, thus carrying hope for better management and intervention.

Hypertension

Hypertension is defined as the persistent elevation in blood pressure (3). The diagnosis is established based on the levels of systolic blood pressure (SBP) and/or diastolic blood pressure (DBP), and this may vary depending on the presence or absence of coexisting comorbidities (4, 5). It is very true that the numbers by which the diagnosis is based are well defined by the WHO and other entities, yet, these numbers may vary from population to another. Other factors may also contribute to the diagnosis, follow up and treatment of hypertension; factors like ethnicity.

Multi-Ethnic Study of Atherosclerosis (MESA) documented the distribution of treated but uncontrolled hypertension and showed hypertension to be significantly higher among ethnic groups of African Americans (35%), Chinese 33%, and Hispanics (32%) compared to Caucasians (24%)(6)

The explanation for the high rates of hypertension and subsequent organ damage phenomena among African Americans is beyond comprehension. ~~It's~~ It has been suggested that socioeconomic factors play a role as well as lifestyle style, clinical factors and not to mention

environmental and genetic factors that may account significantly for these differences and the response to drugs (7-13).

Hypertension is classified as primary or essential and secondary. As shown in ~~table1~~Table 1~~,~~ where the main differences between the causes of the two types are demonstrated~~:~~, causes of the primary hypertension is ~~of~~ unknown ~~causes~~.

Table 1: Classification and some causes of secondary hypertension

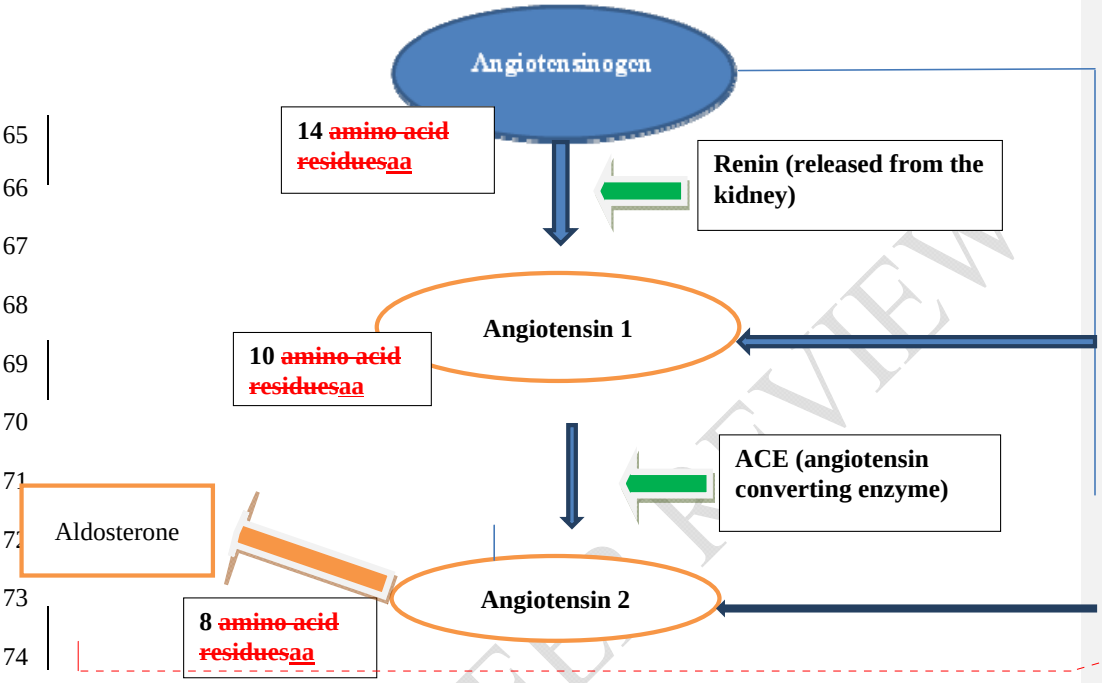
Primary (essential)	Secondary
UNKNOWN CAUSEs	Renovascular disease
	Reno parenchymal
	Pheochromocytoma
	Hyperthyroidism
	Drugs

RAAS over activation is considered to be a load on the cardiovascular system. Angiotensin II will increase the peripheral resistance ~~and~~ as Aldosterone ~~will~~ increases the volume of circulating blood. ~~and b~~Both of these effects will increase pressure.

In response to the elevated load, the heart hypertrophies as a vital mechanism for compensation, and this change is valid for some time before the overload eventually exceeds the heart capacity and the compensation becomes a failure. (2)

The renin-angiotensin system cascades

It has been traditionally accepted the classical pathway of activation of the RAAS as depicted in ~~figure1~~Figure 1.



Comment [uu1]: Figure 1 should been organized with photoshop or illustrator instead of its present view.

Figure 1: Scheme showing the classical cascade of activation of the renin-angiotensin system. aa, amino acid.

As depicted in Figure 2. Recently, as depicted in figure 2, using the combination of protein chemistry and genomics, a discovery is has recently made of new peptides of this system (13), specifically Angiotensin 1-7 (Ang1-7). Therefore, Ang1-7 is considered one of the most intriguing peptides for its formation could be directly from angiotensin I (Ang I) bypassing angiotensin-converting enzyme (ACE) and because it has actions which are often opposing to those conventional effects of Ang II (14).

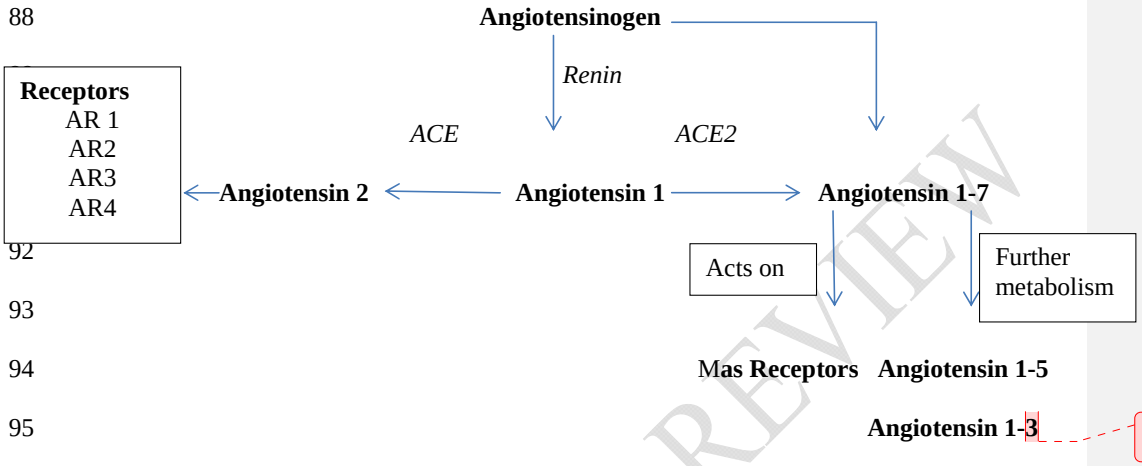


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Figure 2: The alternative cascades of RAS activation

The long identified two primary enzymes of the system ~~long identified~~, ACE and angiotensin-converting enzyme 2(ACE2), have different areas of functioning. For instance, ACE produces angiotensin2 by releasing two amino acids from angiotensin 1~~;~~ whereas ACE2 uses angiotensin 1-9 as a substrate to yield angiotensin 1-7.

Previous studies have displayed that Angiotensin 1-7 targets the heart and the vessels, these actions result in the so-called cardio-protection. (15, 16, 17)

It has been shown that activation of intrinsic (ACE2) would improve endothelial function by decreasing the reactive oxygen species (ROS) production. (18)

The ACE2 gene maps to chromosome Xp22 and contains 18 exons spanning ~40kb of genomic DNA~~ACE 2, the 40kb gene of which is located on chromosome Xp22 and contains 18 exons, .~~ ~~m~~Many of these exons are comparable to those in the ACE gene (19). It was initially

hypothesized that disruption of the delicate balance between ACE and ACE2 would result in abnormal blood pressure control (20~~),~~ ~~).~~ ACE2 might have a protective role against increases in blood pressure, and ~~conversely,~~ ACE2 deficiency might lead to hypertension. The presence of ACE2 in vascular endothelial cells and smooth muscle cells (21) may lead to this conclusion.

Overwhelming evidence indicates that over-activity of systemic as well as of intra-cardiac RAAS leads to myocardial Ang II production, which contributes to the progression of heart failure.

Post-injury heart remodeling or remodeling in response to high or increasing wall stress is a major player in the progression of cardiac physiology deterioration~~,~~ ~~of~~ which eventually leads to heart failure (22, 23)

It is widely accepted that Ang-(1-7) may counteract the negative remodeling processes inflicted by Ang II on the cardiac tissues. The suggested mechanisms are binding to the Mas receptor to activate a sequence of events leading to vasodilation and anti-hypertrophic effects (24)

Li Lin and colleagues from the Department of Cardiovascular Medicine, East Hospital, China, have investigated the effect of both metabolites on the heart of mice. Angiotensin 1-7 inhibited the cardiac fibrosis induced by Ang II in vivo~~.~~ (25). Increased cardiomyocyte autophagy and myocardial fibrosis have been suspected to be vital in the transition from adaptive hypertrophy to maladaptive and eventually to heart failure (26, 27).

Li Lin also demonstrated that treating mice with angiotensin II has advanced effects on heart remodeling. These included the increased left ventricular (LV) anterior wall at the end-diastole, LV posterior wall at the end-diastole, LV internal dimension at end-diastole and decreased LV fractional shortening Gross heart size and heart weight to body weight ratio (HW/BW) were also increased by treatment with Ang II (25). They also documented that~~:~~ these effects were reversed by Angiotensin 1-7 by activating the Mas receptor in their experiment. They even went a step

Comment [uu3]: This sentence is not understood so it should be improved.

further in investigating the oxidative process in the heart. They used an indicator called MDA for lipid peroxidation to estimate the oxidative stress. Ang II increased the process, while Ang 1-7 reduced it.

Therapeutic intervention targeting the RAAS

Several drugs are in use, which target~~ing~~ the RAAS metabolites in order to treat hypertension~~,~~. M~~m~~any of them are known like the ACE inhibitors and its receptor blockers. New agents like direct renin inhibitors and mineralocorticoid receptor antagonists have been used.

Several clinical trials have been using these agents such as Heart Outcomes Prevention Evaluation (HOPE) (28). The Microalbuminuria, Cardiovascular (MICRO-HOPE), and Renal Outcomes in HOPE) (29)

It is well documented that African-Americans have a unique reaction to RAAS blockers in comparison to Caucasians. An explanation for this is a variety of mechanisms, including salt sensitivity, low renin, and high aldosterone levels. (30- 34). Yet, no clinical trials to establish the different responses to these and other drugs in participants in Africa in general and Sudan in particular.

Comment [uu4]: Here, what did you say. Further clarify.

Table 2 demonstrates ~~the sums~~ some of the differences between Angiotensin 2 and Angiotensin 1-7

Table 2: Some of the biological differences between the angiotensin 1-7 and angiotensin 2

	Angiotensin 1-7	Angiotensin 2
1	~~Seven amino acid residues~~7 aa	~~Eight amino acid residues~~8 aa
2	Produced by ACE 2	Produced primarily by ACE 1
3	Acts on Mas receptors	Acts on Angiotensin receptors
4	Induces reverse remodeling [25]	Induces pathological remodeling [25]
5	Anti-apoptotic effect [35]	Induces apoptosis in the infarction area

Discussion

In Africa, and specifically in Sudan, where the highest interethnic variations exist worldwide~~;~~, it will not come as a surprise to find different and novel genes involved in the physiology of hypertension. This wide genetic diversity mandates a research into the genetic portfolio of these populations and applies them to our subpopulations such as whole genome sequencing and other molecular diagnostic tools in order to reveal the DNA variants in our country. Identifying these variants in our subpopulations will evidently lead to a more individualized approach to treating different patients with elevated blood pressure. The choice of drugs acting on the metabolites of RAAS will~~;~~ ultimately~~,~~ change the outcome for patients with HTN, and cardiovascular disease resulting in reduced incidence of heart failure.

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Conclusion:

Understanding the function~~ing~~ of Angiotensin 1-7 in hypertension may optimize current therapies and ultimately guide the development of new therapeutic strategies. Finding new means to stimulate the production of Angiotensin 1-7 will lead to better protection of the heart and, perhaps, other organs from damage. Taking into account DNA variations will affect the design and selection of drugs affecting the system.

Summary

Ang II is not the sole active metabolite of the system. It exerts its actions by binding to receptors distributed throughout the body, heart, vessels, brain and other organs. Ang 1-7 is another active metabolite and it ~~has~~ binds to~~the~~ Mas receptors with various distributions. Ang 1-7 could be produced by ACE2 and by bypassing ACE1. Ang 1-7 counteracts the effects of Ang II on heart and vessels in particular through many mechanisms (biochemical, physiological and structural reverse remodeling). Bearing in mind the genetic diversity among different ethnic groups, a population-based approach in treating hypertension should have priority eventually.

References

1. Roberts CS, MacLean D, Maroko P, Kloner RA. Early and late remodeling of the left ventricle after acute myocardial infarction. Am J Cardiol. 1984; 54:407–410. [PubMed: 6235736]
2. Lorell BH. Transition from hypertrophy to failure. Circulation 1997; 96:3824–3827.
3. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ. Seventh report of the Joint National

Comment [uu7]: More recent papers are available on https://www.ncbi.nlm.nih.gov/pubmed/?term=Angiotensin+1-7. Adding them to paper will help improve the quality of paper. Please refers to this link https://www.ncbi.nlm.nih.gov/pubmed/?term=Angiotensin+1-7.

Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42: 1206-1252 [PMID: 14656957 DOI: 10.1161/01.HYP.0000107251.49515.c2]

4. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens* 2013; 31: 1925-1938 [PMID: 24107724 DOI: 10.1097/HJH.0b013e328364ca4c]
5. Kramer H, Han C, Post W, Goff D, Diez-Roux A, Cooper R, Jinagouda S, Shea S. Racial/ethnic differences in hypertension and hypertension treatment and control in the multi-ethnic study of atherosclerosis (MESA). *Am J Hypertens* 2004; 17: 963-970 [PMID: 15485761 DOI: 10.1016/j.amjhy-per.2004.06.001]
6. Tarver-Carr ME, Powe NR, Eberhardt MS, LaVeist TA, King-ton RS, Coresh J, Brancati FL. Excess risk of chronic kidney disease among African-American versus white subjects in the United States: a population-based study of potential explanatory factors. *J Am Soc Nephrol* 2002; 13: 2363-2370 [PMID:12191981 DOI: 10.1097/01.ASN.0000026493.18542.6A]
7. Norris K, Nissenson AR. Race, gender, and socioeconomic disparities in CKD in the United States. *J Am Soc Nephrol* 2008; 19: 1261-1270 [PMID: 18525000 DOI: 10.1681/ASN.2008030276]
8. Freedman BI, Murea M. Target organ damage in African American hypertension: the role of APOL1. *Curr Hypertens Rep* 2012; 14: 21-28 [PMID: 22068337 DOI: 10.1007/s11906-011-02 37-4]

9. Martins D, Norris K. Hypertension treatment in African Americans: physiology is less important than sociology. *Cleve Clin J Med* 2004; 71: 735-743 [PMID: 15478705 DOI: 10.3949/ ccjm.71.9.735]
10. Norris K, Francis C. Gender and ethnic differences and considerations in cardiovascular risk assessment and prevention in African Americans. Practical Strategies Pre Heart Dis, 2004: 415-440
11. Suthanthiran M, Li B, Song JO, Ding R, Sharma VK, Schwartz JE, August P. Transforming growth factor-beta 1 hyperexpression in African-American hypertensives: A novel mediator of hypertension and/or target organ damage. *Proc Natl Acad Sci USA* 2000; 97: 3479-3484 [PMID: 10725360]
12. Ferdinand KC, Townsend RR. Hypertension in the US Black population: risk factors, complications, and potential impact of central aortic pressure on effective treatment. *Cardiovasc Drugs Ther* 2012; 26: 157-165 [PMID: 22246101 DOI: 10.1007/ s10557-011-6367-8]

13. Albiston AL, McDowall SG, Matsacos D et al. (2001). Evidence that the angiotensin IV (AT(4)) receptor is the enzyme insulin-regulated aminopeptidase. Journal of Biological Chemistry, 276: 48623-48626.

Santos RAS Campagnole'Santos MJ & Andrade SP. Angiotensin (1-7): an update. Regulatory peptide. 2000. 91.45:62

14. Brosnihan KB, Li P & Ferrario CM (1996). Angiotensin-(1-7) dilates canine coronary arteries through Kinins and nitric oxide. *Hypertension*, 27 (Part 2): 523-528
15. Ferreira AJ, Santos RAS & Almeida AP (2001). Angiotensin-(1-7): cardioprotective effect in

myocardial ischemia/reperfusion. *Hypertension*, 38 (Part 2): 665-668.

16. Loot AE, Roks AJM, Henning RH, Tio RA, Suurmeijer AJH, Boomsma F & van Gilst WH (2002). Angiotensin-(1-7) attenuates the development of heart failure after myocardial infarction in rats. *Circulation*, 105: 1548-1550
17. Fraga-Silva RA(1), Costa-Fraga FP, Murça TM, Moraes PL, Martins Lima A, LautnerRQ, Castro CH, Soares CM, Borges CL, Nadu AP, Oliveira ML, Shenoy V, Katovich MJ,Santos RA, Raizada MK, Ferreira AJ. Angiotensin-converting enzyme 2 activation improves endothelial function. Hypertension. 2013 Jun;61(6):1233-8. doi: 10.1161/HYPERTENSIONAHA.111.00627. Epub 2013 Apr 22
18. Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. J Biol Chem.2000; 275(43):33238-33243
19. Yagil Y, Yagil C. Hypothesis: ACE2 modulates blood pressure in the mammalian organism. Hypertension.2003; 41(4):871-873
20. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, Van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. The first step in understanding SARS pathogenesis. J Pathol.2004; 203(2):631-637
21. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation. 1990; 81:1161–72. [PubMed: 2138525]
22. Sharpe, N. Cardiac Remodeling in Congestive Heart Failure. In: Hosenpud, JD.; Greenberg, BH, editors. Congestive Heart Failure. 2. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 101-15.

23. Marangoni RA, Carmona AK, Passaglia R, et al. Role of the kallikrein-kinin system in Ang-(1-7)-induced vasodilation in mesenteric arterioles of Wistar rats studied in vivo-in situ. Peptides. 2006; 27: 1770–5.

24. Flores-Munoz M, Godinho BMDC, Almalik A, et al. Adenoviral delivery of angiotensin-(1-7) or angiotensin-(1-9) inhibits cardiomyocyte hypertrophy via the Mas or angiotensin type 2 receptor. PLoS ONE. 2012; 7: e45564.

25. Li Lin , Xuebo Liu , Jianfeng Xu , Liqing Weng , Jun Ren , Junbo Ge , Yunzeng Zou. Mas receptor mediates cardioprotection of angiotensin-(1-7) against Angiotensin II-induced cardiomyocyte autophagy and cardiac remodeling through inhibition of oxidative stress. J. Cell. Mol. Med. Vol 20, No 1, 2016 pp. 48-57

26. Zhu HX, Tannous P, Johnstone JL, et al. Cardiac autophagy is a maladaptive response to hemodynamic stress. J Clin Invest. 2007; 117: 1782–93.

27. Bayes-Genis A, de Antonio M, Vila J, et al. Head- to- head comparison of 2 myocardial fibrosis biomarkers for long-term heart failure risk stratification. J Am Coll Cardiol. 2014; 63: 158–66.

28. Yusuf S, Sleight P, Pogue J, *et al.*: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med.* 2000; 342(3): 145–53

29. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet.* 2000; 355(9200): 253–9.

30. Cruickshank JK, Anderson NM, Wadsworth J, *et al.*: Treating hypertension in

black compared with white non-insulin dependent diabetics: a double-blind trial of verapamil and metoprolol. *BMJ*. 1988; 297(6657): 1155–9.

31. Preston RA, Materson BJ, Reda DJ, et al.: Age-race subgroup compared with renin profile as predictors of blood pressure response to antihypertensive therapy. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. JAMA. 1998; 280(13): 1168–72.
32. Weir MR, Chrysant SG, McCarron DA, et al.: Influence of race and dietary salt on the antihypertensive efficacy of an angiotensin-converting enzyme inhibitor or a calcium channel antagonist in salt-sensitive hypertensives. Hypertension. 1998; 31(5): 1088–96.
33. Helmer OM: The renin-angiotensin system and its relation to hypertension. Prog Cardiovasc Dis. 1965; 8(2): 117–28.
34. Chrysant SG, Danisa K, Kem DC, et al.: Racial differences in pressure, volume and renin interrelationships in essential hypertension. Hypertension. 1979; 1(2): 136–41.
35. Xiang Xiao, Cheng Zhang, Xiaotang Ma, Huilai Miao, Jinju Wang, Langni Liu, Shuzhen Chen, Rong Zeng, Yanfang Chen, and Ji C. Bihl. Angiotensin-(1-7) Counteracts Angiotensin II-induced Dysfunction in Cerebral Endothelial Cells via Modulating Nox2/ROS and PI3K/NO Pathways. *Exp Cell Res*. 2015 August 1; 336(1): 58–65. doi:10.1016/j.yexcr.2015.06.010.