

Physiological Effects of Angiotensin III

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ABSTRACT

The Renin Angiotensin System (RAS) is a peptide hormone system that has many physiological effects. In addition to this it plays an important role in the pathophysiology of many diseases, such as hypertension, Congestive Heart Failure (CHF), Myocardial Infarction (MI) and diabetic nephropathy. The main biologically active peptides of RAS are Angiotensinogen (AGT), Angiotensin II (Ang II), Angiotensin III (Ang III), Angiotensin IV (Ang IV) and Angiotensin [Ang-(1-7)]. Even though, Ang II is still considered the major peptide of the RAS, there is growing evidence that peptide fragments of Ang II like Ang III also have various and important physiologic roles. Moreover, most of the available studies have focused on Ang II as the likely key peptide from the RAS that directly and indirectly regulates physiological functions. However, findings from recent studies suggest that Ang III may produce physiologically relevant effects that are similar to those produced by Ang II. Ang III is heptapeptide and has about 40% of the vasopressin activity of Ang II, but 100% of the aldosterone-stimulating activity. It has been suggested that Ang III is the natural aldosterone-stimulating peptide. However, this appears not to be the case and instead Ang III is simply a breakdown product with some biologic activity. Therefore, this research review focuses on Ang III and physiological effects that it produces in the body. This review is also expected to focus on the recent knowledge of Ang III and physiologic effects in various parts of human body.

Key words: Physiology, Angiotensin III, Its effects.

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History

- Submission Date: 07-11-2018;
- Review completed: 10-12-2018;
- Accepted Date: 19-12-2018.

DOI : 10.5530/ijcep.2018.5.4.15

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INTRODUCTION

Ang III is a physiological relevant peptide of RAS. Ang II is metabolized rapidly to Ang III by Aspartyl Aminopeptidase A (APA). An APA removes the aspartic acid (Asp) residue from the amino terminal of the peptide. The resulting heptapeptide is Ang III and it has many physiologic activities. Removal of a second amino terminal residue from Ang III produces the hexapeptide sometimes called Ang IV, which is also said to have some activity. Most, if not all, of the other peptide fragments that are formed are inactive. In addition, aminopeptidase can act on angiotensin I to produce (des-Asp¹) angiotensin I and this compound can be converted directly to angiotensin III by the action of ACE. Angiotensin-metabolizing activity is found in red blood cells and many tissues. Many researchers have investigated the physiologic function of Ang III.

EFFECTS OF ANGIOTENSIN III

Cardiovascular effects of angiotensin III

A recent study investigated that Ang III has cardioprotective effects i.e. it protects the heart against Ischemia/Reperfusion (I/R) injury. This research finding indicated that Ang III markedly decreased myocardial infarct size, lactate dehydrogenase levels, increased coronary flow and the concentrations of

atrial natriuretic peptide in coronary effluent during reperfusion. The result of this experimental research suggested that the cardioprotective effects of Ang III against I/R injury may be partly related to activating antioxidant and antiapoptotic enzymes via Ang II type 2 receptor (AT₂R) and ATP-sensitive K⁺ channel (K⁺ATP).^[1]

Inhibition of brain angiotensin III attenuates sympathetic over activity and cardiac dysfunction in rat's post-myocardial infarction. This finding showed that brain APA and Ang III appear to play a central role in the sympathetic over activity and left ventricular dysfunction in rats post-myocardial infarction.^[2] Ang II, a characteristically potent vasoconstrictor, primarily vasodilates the adrenal vasculature. This primary vasodilatation in adrenal arteries is unique to the adrenal circulation and has potentially important implications in the regulation of adrenal blood flow and steroidogenesis after stimulation of Ang II. Endothelial metabolism of Ang II to Ang III, augments the vasorelaxation response in adrenal cortical arteries. Thus, this finding indicated that aminopeptidase metabolism of Ang II to Ang III leads vasodilation which intern increases adrenal blood flow after Ang II stimulation.^[3] Evidence has also showed that Ang III has only 25-50% the vasoconstrictor activity of Ang II.^[4]

Cite this article: Tolessa D, Chala A, Haji K, Mamo G, Eshetu G. Physiological Effects of Angiotensin III. Int J Clin Exp Physiol. 2018;5(4):164-7.

Aldosterone release and renal effects of angiotensin III

Several studies have reported that Ang III also stimulates aldosterone release and increases circulating aldosterone levels.^[5,6] Evidence revealed that Ang III has a faster onset of action and is slightly more potent than angiotensin II in stimulating the release of aldosterone from dispersed cells of the adrenal cortex. Ang III is as potent as or a more potent stimulus of aldosterone biosynthesis in zona glomerulosa of adrenal cortex than Ang II. Ang III-stimulated aldosterone release seems to be mediated partially by AT₂R and not Ang II Type 1 Receptor (AT₁R). This study revealed that Ang III stimulates Aldosterone secretion from zonal glomerulosa of adrenal cortex partially via AT₂R but not AT₁R.^[7-9] Ang III is less potent than Ang II in evoking dopamine, epinephrine and norepinephrine from adrenal medulla.^[10] Ang III produces a decrease in plasma renin activity similar to that caused by Ang II.^[11]

Research finding reported that Ang III is equipotent to Ang II with regard to renal functions and these Ang III effects are mediated through AT₂R. This study also showed that the metabolic clearance rate of Ang III is five times that of Ang II.^[12] Studies examined that Renal Interstitial (RI) Ang III infusion induces natriuresis and AT₂R translocation in Wistar-Kyoto (WKYs) but not in Spontaneously Hypertensive Rats (SHRs). This finding indicates that in WKYs, RI Ang III infusion elicits natriuresis (urine sodium excretion rate increased) and renal proximal tubule cell AT₂R translocation in WKYs but identical conditions failed to increase the urine sodium excretion rate in SHRs suggesting that defects in AT₂R-mediated natriuresis and trafficking may be important to the development of hypertension in SHRs.^[13] Moreover, in the kidney, Ang II is metabolized to Ang III by Aminopeptidase A (APA). The conversion of renal Ang II to Ang III is critical for AT₂ receptor-mediated natriuresis in rats.^[14]

Central nervous system effects of angiotensin III

Many investigators have established that Ang III have important cellular effects and the active peptide in the central nervous system. The physiologically relevant peptide in the brain that binds to and activates the AT₁ receptor is Ang III, not Ang II. A research finding suggests that Ang III directly induce phosphorylation of Mitogen-activated Protein (MAP) kinases similar to Ang II as well as growth of astrocyte in brainstem and cerebellum. These findings concluded that Ang III was as biologically active and similar intracellular and physiological effects as Ang II.^[15] Findings from several studies have also shown that centrally produced Ang II is rapidly degraded by many enzymes (primarily APA), leading to the accumulation of Ang III. Moreover there are studies which mainly focus on the degradation of Ang II to Ang III by APA which is most known metabolic pathway for Ang II. Ang III binding was tighter and more widely distributed in many regions of the brain in all species so far examined than is the case for Ang II. In the rat, the dipsogenic and vasopressin potencies of Ang III and Ang II were the same at intracranial doses below approximately 10 pmol and in the gerbil, water intakes were larger after Ang III than after Ang II.^[16,17] Ang III is more potent than Ang II in stimulating tyrosine hydroxylase in adrenergic nerves and brain.^[6]

Effects of angiotensin III on prostaglandin release

There was study conducted to examine the ability of the angiotensins (Ang I, Ang II, Ang III) to release a Prostaglandin E (PGE)-like substance in the isolated Krebs' perfused kidney and mesenteric vasculature of the rabbit by parallel bioassay. The finding of this study revealed that in the kidneys, Ang III was less potent for PGE release than Ang II but more potent than Ang I.

In the mesenteric preparation, on the other hand, Ang III more potent than Ang II and Ang I.^[18]

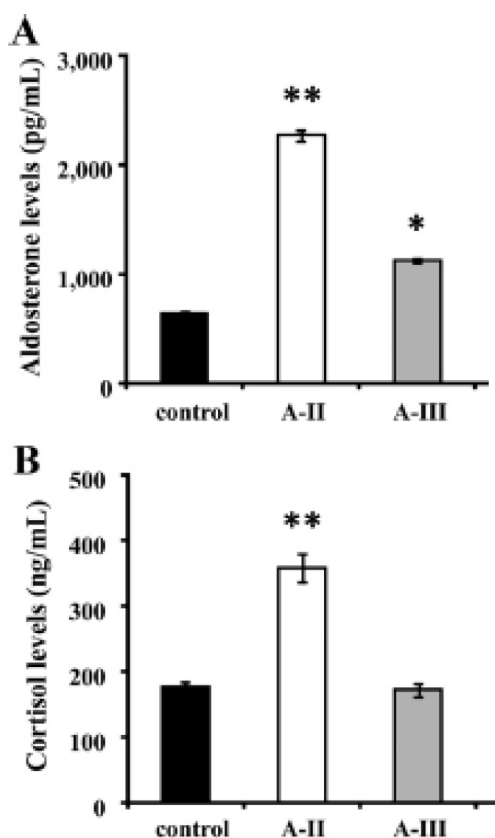


Figure 1: Effect of A-II and A-III on aldosterone or cortisol production.

*, $P < 0.05$ vs. control, $n = 4$; **, $P < 0.01$ vs. control, $n = 4$.

Angiotensin III effects on steroid production

It is well known that ovarian RAS is involved in the production of steroid.^[19-21]

Few experimental findings indicate that Ang III is the main peptide involved in ovarian Progesterone (but not Estrogen) production in the rat. A highly significant increase of serum progesterone levels in N-Methyl Nitrosourea (NMU)-treated rats, concomitantly with an increase in ovarian aspartyl and glutamyl aminopeptidase activities. This finding concluded as the relationship between ovarian RAS and progesterone overproduction in a rat model of mammary carcinogenesis indicates ovarian RAS as a new potential target in breast cancer therapy.^[22-23] Ang III significantly stimulated aldosterone production by 1.8 times but had no effect on cortisol production (Figure 1).^[24]

BIOCHEMISTRY OF ANGIOTENSIN III

Ang III is a heptapeptide composed of Arginine, Valine, Tyrosine, Isoleucine, Histidine, Proline and Phenylalanine amino acids. It is expressed in many tissues such as heart, blood vessels, brain, kidney, liver and adrenal glands. Ang III is obtained by deletion of the N-terminal aspartic residue by glutamyl-aminopeptidase and aspartyl aminopeptidase.

SYNTHESIS OF ANGIOTENSIN III

Different angiotensin peptides are formed by the rennin angiotensin system (see Figure 2). Ang III is a dipsogenically active peptide produced by the breakdown of Ang II by amino peptidase in many tissues. Aminopeptidase A preferentially cleaves N-terminal acidic amino acids from A-II to form A-III. Ang III is obtained by deletion of the N-terminal aspartic residue by glutamyl-aminopeptidase and aspartyl-aminopepti-

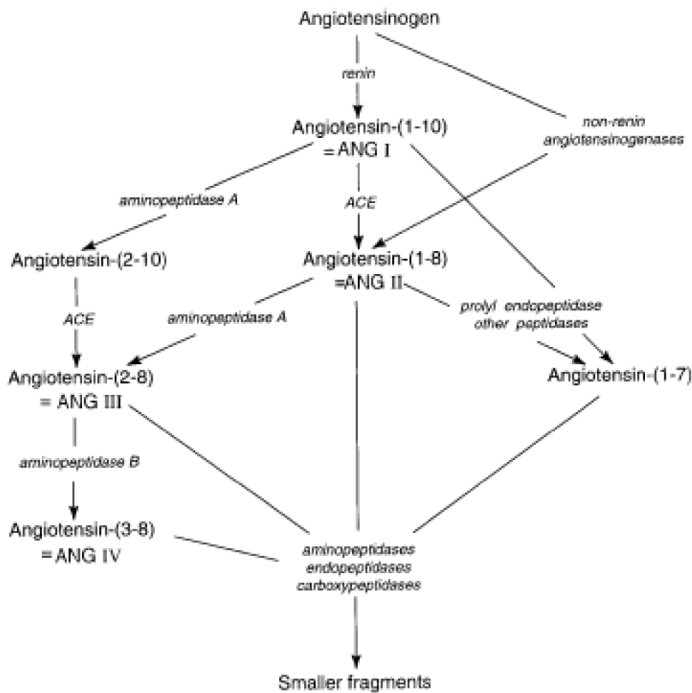


Figure 2: Schematic diagram of the metabolism of Ang II and formation of Ang III.

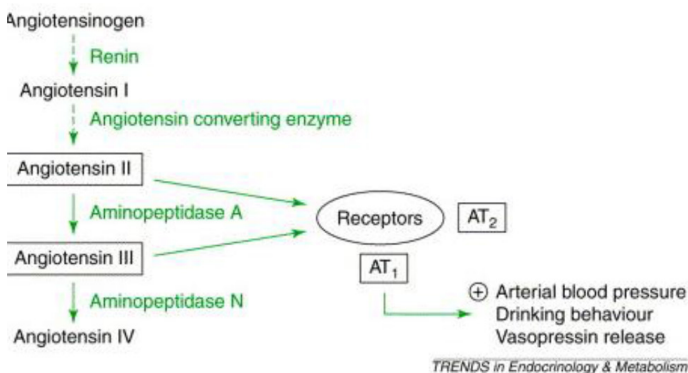


Figure 3: Mechanism of action of Ang III.

dase. Both enzymes are named together as aminopeptidase A (APA). It is most likely produced in tissue with high levels of Aminopeptidases A, such as brain and kidney tissues.^[25]

MECHANISM OF ACTION OF ANGIOTENSIN III

Ang III brings about physiologic response first by binding to AT_1R and AT_2R . AT_1R and AT_2R G-coupled polypeptide that contain approximately 360 amino acids and span cell membrane about seven times. AT_1R found in heart, blood vessels, brain, kidney, liver and adrenal glands of healthy adult. AT_2R is found ubiquitously in the fetus, where it regulates normal organ development. In adult, it is only present in adrenal medulla, uterus, ovary, vascular endothelium and distinct brain areas. Ang III act on both AT_1R and AT_2R and display similar affinities for both AT_1R and AT_2R ^[26-28] It has been reported that Ang III appears to be a preferred activator of AT_2R in the heart^[29,30] coronary circulation and kidney.^[31,32] Experimental studies showed that in highly stretched atria and *in vivo* experiments, Ang III have stimulatory effect on ANP secretion via AT_2R .^[33,34] Research finding also reported that Ang III is critical for AT_2R -mediated natriuresis.^[14] Ang III has been shown to be major effectors peptide expressed in the brain. In the brain, Ang III is responsible for mediating vasoconstriction and to increase arterial blood pressure via the AT_1R . Ang III was also shown to mediate Antidiuretic (ADH) release when administered directly into the third ventricle of the brain^[35-40] Similarly, Ang III stimulates aldosterone production in addition to Ang II (Figure 3), (Figure 4).^[41]

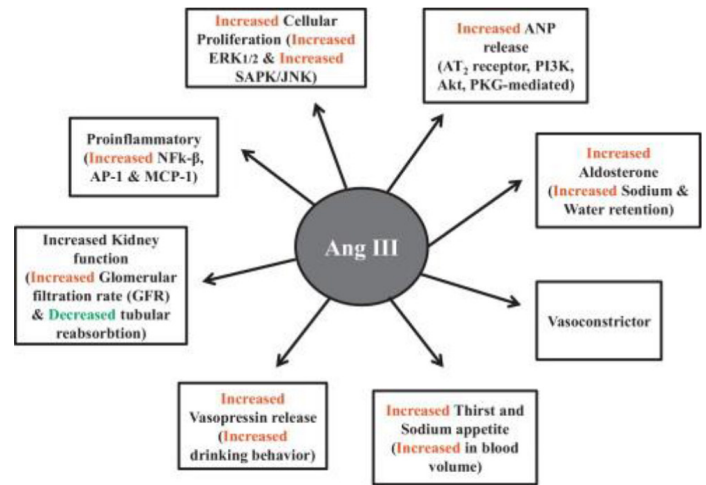


Figure 4: Mechanism of action of Ang III.

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CONCLUSION

Although Ang III have an important role almost as equipotent as Ang II in many tissues such as in kidney, brain, heart, glands and vessels, very few current studies discussed the important of Ang III. Thus, this review is thought to capture the attention of many researchers to extensively focus on Ang III leading to discovery of new evidences of this peptide and its physiologically relevant roles and pathophysiology of various diseases.

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Cite this article: Tolessa D, Chala A, Haji K, Mamo G, Eshetu G. Physiological Effects of Angiotensin III. *Int J Clin Exp Physiol.* 2018;5(4):164-7.