INTERNATIONAL RESEARCH JOURNAL OF PHARMACY **ISSN 2230 – 8407**
Available online http://www.irjponline.com
Review Article

RENIN ANGIOTENSIN SYSTEM AND MALIGNANCY: A MINI REVIEW

Jisha M. Lucca*[1], Nathani Minaz [2], Nazeer Ahamed [3]
[1]Asst. Professor. Department of Pharmacy Practice, Bharat Institute of Technology- Pharmacy, Hyderabad, AP, India
[2]Asst. Professor. Department of Pharmacology, Bharat Institute of Technology- Pharmacy, Hyderabad, AP, India
[3]Asst. Professor. Department of Pharmacology, Vignan institute of pharmaceutical sciences, Hyderabad, AP, India

Article Received on: 12/05/11 Revised on: 20/06/11 Approved for publication: 07/07/11

*Jisha. M. Lucca, Asst Professor, Dept. Pharmacy Practice, Barath Institute of technology. Hyderabad .AP
Email.jishajojo06@yahoo.co.in, jispharm@gmail.com

ABSTRACT
Cancer is the leading cause of death worldwide (World Health Organization). Therapeutic strategies usually involve a combination of surgical ablation, radiotherapy and chemotherapy. Apart from conventional chemotherapy, targeting of the tumour vasculature by vascular disrupting agents or inhibitors of angiogenesis has also been used. Several antihypertensive agents have been used to reduce the incidence and mortality of malignancy. We therefore tried to analyze the available data regarding the relationship between rennin angiotensin system and malignancy. The renin–angiotensin system is usually associated with its systemic action on cardiovascular homoeostasis. However, recent studies suggest that at a local tissue level, the renin–angiotensin system influences tumour growth. Several paracrine mechanisms existing at local tissue sites have been implicated in tumourigenesis. One such system is the renin–angiotensin system that exists in several organs at a local tissue level. Epidemiological and experimental studies now suggest that the renin–angiotensin system may contribute to the paracrine regulation of tumourigenesis. Blockade of the renin–angiotensin system may, therefore, provide an alternative, adjunctive therapy for the treatment of solid tumours.
KEYWORDS: Renin–angiotensin system, Tumour, Angiogenesis, Apoptosis

INTRODUCTION

The renin angiotensin aldosterone system (RAAS) has an important role in the regulation of blood pressure and fluid electrolyte balance. Ang II is the main effector of the renin–angiotensin system (RAS) system, which has been shown to play an important role in the regulation of vascular homeostasis, with various implications for both cardiovascular diseases and tumour angiogenesis[1]. It exerts its various actions to the cardiovascular and renal systems via two seven transmembrane domain receptors termed as angiotensin II type 1 receptor (AT1) and angiotensin II type 2 receptor (AT2) showing a complex pattern of regulation and function[2-5]. In rat and mouse, two AT1 subtypes have been cloned and characterized; they are termed AT1A and AT1B[6]. The AT1 and AT2 subtypes show similar properties of ANG II binding but different genomic structure and localization as well as tissue-specific expression and regulation[2]. AT1 receptors are expressed in various parts of the body and are associated with their respective functions, such as blood vessels, adrenal cortex, liver, kidney and brain, while AT2 receptors are highest in fetal mesenchymal tissue, adrenal medulla, uterus and ovarian follicles [7]. The opposing roles of the AT1 and AT2 receptors in maintaining blood pressure, water and electrolyte homeostasis are well established. Rudolf Virchow discovered Tumour has been linked with inflammation and study shows that the renin-angiotensin system is a key mediator of inflammation, with the AT receptors governing the transcription of pro-inflammatory mediators both in resident tissue and in infiltrating cells such as macrophages[8]. Whereas most of the well-known actions of ANG II such as vasoconstriction and aldosterone release are mediated by the AT1 receptor, the AT2 receptor has been considered to be more of an enigma[9,10]. It appears to play an important functional role in prenatal development, and in the adult, AT2-mediated actions has been shown to counteract AT1 effects such as cell proliferation in vitro[11] and in vivo[12]. Increasing evidence supports a role of AT2 particularly in the regulation of growth, differentiation, and regeneration of neuronal tissue[13]. The over expression of the vasoconstrictor AT1 was reported in association with human cancers of the breast[14], pancreas[15], kidney[16], squamous cell carcinoma[17], keratoacanthoma[17], larynx [18], adrenal gland[18], and lung[19]. AT2 has been identified as

expressed in preference to AT1 in only on colorectal cancer [20].

The actions, mediated via the Ang II type 1 receptor (AT1R), lead to the idea that Ang II may play a role in cancer, and experimental evidence indicates that angiotensin converting enzyme inhibitors and AT1R blockers have beneficial effects on tumor progression, vascularization, and metastasis[21–23]. Further, numerous studies have shown antigrowth and antiproliferative effects of Ang II via Ang II type 2 receptor (AT2R), in opposition to actions of this peptide via the AT1R [24]. Thus, there may be a potential beneficial role of AT2R in cancer, and this idea is supported by data that indicate that pheochromocytoma growth is inhibited by AT2R activation[25].

Mechanism for Antiangiogenic Effect of RAS

Angiogenesis and apoptosis are primordial features of malignant tumours, constituting attractive therapeutic targets; drugs that inhibit angiogenesis or promote apoptosis could be associated with cytotoxic agents to improve antitumor therapy. The fact that multifunctional hormonal systems, such as the renin– angiotensin–aldosterone system, influence tumour growth and angiogenesis provides interesting pathways to the study of cancer. The antineoplastic activity obtained by the selective blockage of AT1 in malignant glioma seems to be mediated by two different mechanisms, inhibition of the synthesis of growth factors and promotion of apoptosis, providing a potential therapeutic adjuvant for malignant gliomas. The earlier studies carried out in PC-12 cells (a rat pheochromocytoma cell line) have suggested that programmed cell death is mediated by the AT2 receptor[26]. The ANG II can stimulate angiogenesis, acting via AT1 receptors within the subcutaneous sponge granuloma model in the rat and that AT1 and AT2 receptors and ACE develop sequentially during microvascular maturation[27]. This confirms earlier reports that ANG II stimulates angiogenesis in the chick embryo model[28, 29]. Silvestre et al,[30] indicated that AT2 confers an antiangiogenic effect that is associated with activation of apoptosis. The selective blockage of AT1 may lead to disequilibrium of AT1/AT2 relation that promotes AT2 receptor stimulation which, in turn, could increase its proapoptotic effects.

Previously Conducted Study Result

The AT1 blocker losartan has been shown to antagonize platelets, which are thought to modulate cell plasticity and angiogenesis via the vascular endothelial growth factor (VEGF) [31].It has been postulated that losartan and other AT1 blockers can act as novel anti-angiogenic, anti-invasive and anti-growth agents against neoplastic tissue[31]. Furthermore, it has been shown that angiotensin II induces the phosphorylations of mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 3 (STAT3) in prostate cancer cells. In contrast, AT1 inhibitors have been shown to inhibit the proliferation of prostate cancer cells stimulated with EGF or angiotensin II, through the suppression of MAPK or STAT3 phosphorylations[32]. Angiotensin II also induces (VEGF), which plays a pivotal role in tumour angiogenesis and has been the target of various therapeutics, including antibodies and aptamers[33]. Although the role of angiotensin II in VEGF-mediated tumour development has not yet been elucidated, an ACE inhibitor significantly attenuated VEGF-mediated tumour development, accompanying the suppression of neovascularisation in the tumour and VEGF-induced endothelial cell migration[34]. Perindopril, another ACE inhibitor has also been shown to be a potent inhibitor of tumour development and angiogenesis through suppression of the VEGF and the endothelial cell tubule formation[35]. A retrospective study based on 5207 patients found that the incidence of fatal cancers was reduced in patients treated with ACE inhibitors for 3 years[36].A reduced risk of developing esophageal (55%), pancreatic (48%) and colon cancer (47%) was observed in an assessment of 483 733 veterans, 38% of which were taking ACE inhibitors[37]. Candesartan was reported to reduce tumour related angiogenesis and the number of lung metastases in a murine lung cancer model[38]. In a mouse model of colorectal cancer liver metastases, both captopril and irbesartan decreased tumour growth, the percentage of liver metastases and tumour-associated angiogenesis[39]. Additionally, a study undertaken in 1998 suggested that hypertensive patients taking ACE inhibitors were significantly less at risk of developing cancer than those taking other hypertensive treatments[40].

The local RAS exerts diverse actions in many organs. In some tissues they appear to be regulated independently. The observations presented here suggest that the ability of increased AT2R expression to induce apoptosis in prostate cancer cells may have potential therapeutic implications for this disease, and suggest that AT2R is a promising novel target gene for prostate cancer gene therapy. In summary, we have made the novel observation that over expression of AT2R in prostate cancer cell lines results in a powerful apoptotic action. The therapeutic value of this observation remains to be assessed, but the fact that similar over expression of AT2R in normal prostate cells does not elicit apoptotic cell death suggests that the strategy of targeting

this angiotensin receptor subtype in prostate cancer may be promising.

CONCLUSION

ARBs can consider a noteworthy anticancer and anti-angiogenesis therapeutic option. From review of the current disease literature, it has been demonstrated that the role of AT1 and AT2 in is not limited to Angiogenesis and apoptosis of a particular cancer but is generally consistent and system wide. There have been several studies that investigated antitumor effects of ARBs throughout anti-angiogenesis. Then also further studies are needed to investigate the molecular mechanisms of AT1 receptor antagonists in cancer cell. It is anticipated that manipulation of the angiotensin system with existing anti-hypertensive drugs could provide a new approach for the treatment of many of the diseases that afflict mankind.

REFERENCES

1. Thomas WG, Mendelsohn. FAO: Molecules in Focus Angiotensin receptors: form and distribution. IJBCB 2003, 35:774-779.
2. De Gasparo M, Catt KJ, Inagami T, Unger T. International Union of Pharmacology.The angiotensin II receptors. Pharmacol Rev 2000; 52: 415–472.
3. Iwai N, Inagami T. Identification of two subtypes in the rat type I angiotensin II receptor. FEBS Lett1992; 298: 257–260.
4. Kaschina E,Unger T. Angiotensin AT1/AT2 receptors: regulation, signalling and function. Blood Press 2003; 12: 70–88.
5. Sayeski PP,Bernstein KE. Signal transduction mechanisms of the angiotensin II type AT(1)-receptor: looking beyond the heterotrimeric G protein paradigm. J Renin Angiotensin Aldosterone Syst 2001; 2: 4–10.
6. Inagami T. Recent progress in molecular and cell biological studies of angiotensin receptors. Curr Opin Nephrol Hypertens 1995; 4: 47–54
7. Thomas WG, Mendelsohn FAO: Molecules in Focus Angiotensin receptors: form and distribution. IJBCB 2003; 35:774-779.
8. Balkwill F, Mantovani A: Inflammation and cancer: back to Virchow? Lancet 2001; 357:539-545.
9. Suzuki Y, Ruiz-Ortega M, Lorenzo O, Ruperez M, Esteban V, EgidoJ. Inflammation and angiotensin II. IJBCB 2003; 35:881-900.
10. Levy BI. Can angiotensin II type 2 receptors have deleterious effects in cardiovascular disease? Implications for therapeutic blockade of the renin-angiotensin system. Circulation 2004; 109: 8–13.
11. Unger T. The angiotensin type 2 receptor: variations on an enigmatic theme. J Hypertens 1999;17: 1775–1786
12. Stoll M, Steckelings UM, Paul M, Bottari SP, Metzger R, Unger T. The angiotensin AT2-receptor mediates inhibition of cell proliferation in coronary endothelial cells. J Clin Invest 1995;95: 651– 657.
13. Morishita R, Gibbons GH, Ellison KE, Nakajima M, Zhang L, Kaneda Y, Ogihara T et al. Single intraluminal delivery of antisense cdc2 kinase and proliferating-cell nuclear antigene oligonucleotides results in chronic inhibition of neointimal hyperplasia. Proc Natl Acad Sci USA1993; 90: 8474–8478.
14. Steckelings UM, Kaschina E, Unger T. The AT2 receptor: a matter of love and hate. Peptides 2005; 26: 1401–1409.
15. Tahmasebi M, Puddefoot JR, Inwang ER, Goode AW, Carpenter R, Vinson GP: Transcription of the prorenin gene in Normal and Diseased Breast. Eur J Cancer 1998; 34:1777-1782.
16. Fujimoto Y, Sasaki T, Tsuchida A, Chayama K: Angiotensin II type 1 receptor expression in human pancreatic cancer and growth inhibition by Angiotensin type 1 receptor antagonist. FEBS Letters 2001; 495:197-200.
17. Goldfarb A, Diz I, Tubbs R, Ferrario M, Novick C: Angiotensin II receptor subtypes in the human renal cortex and renal cell carcinoma. J Urol 1994; 151Supp1:208-13.
18. Takeda H, Kondo S: Differences between Squamous Cell Carcinoma and Keratoacanthoma in Angiotensin Type-1 Receptor Expression. American Journal of Pathology 2001; 158:1633-1637.
19. Marsigliante S, Resta L, Muscella A, Vinson GP, Marzullo A, Storelli C. AT1 antagonist II receptor subtype in the human larynx and squamous laryngeal carcinoma. Cancer Letters 1996; 110:19-27.
20. Batra V, Gropalakrish V, McNeill J, Hickie R. Angiotensin II elevates cytosolic free calcium in human lung adenocarcinoma cells via activation of AT1 receptors. J Urol 1994; 151:208-213.
21. Gary Robert Smith, Sotiris Missailidis. Cancer, inflammation and the AT1 and AT2 receptors. Journal of Inflammation 2004;1:1-3
22. Uemura H, Ishiguro H, Kubota Y. Angiotensin II receptor blocker: possibility of antitumor agent for prostate cancer. Mini Rev Med Chem 2006; 6:835–44.
23. Uemura H, Ishiguro H, Kubota Y. Pharmacology and new perspectives of angiotensin II receptor blocker in prostate cancer treatment. Int J Urol 2008; 15:19–26.
24. Uemura H, Nakaigawa N, Ishiguro H, Kubota Y. Novel molecular targeting therapeutics for prostate cancer. Nippon Rinsho 2005; 63:339–44.
25. Wolf G, Harendza S, Schroeder R. Angiotensin II's antiproliferative effects mediated through AT2-receptors depends on down-regulation of SM-20. Lab Invest 2002; 82:1305–17.
26. Meffert S, Stoll M, Steckelings UM, Bottari SP, Unger T. The angiotensin II AT2 receptor inhibits proliferation and promotes differentiation in PC12W cells. Mol Cell Endocrinol 1996; 122:59–67.
27. Yamada T, Horiuchi M, and Dzau VJ. Angiotensin II type 2 receptor mediates programmed cell death. *Proc* Natl Acad Sci USA1996; 93: 156–160.
28. Walsh DA, Hu DE, Wharton J, Catravas JD, Blake DR, and Fan TP. Sequential development of angiotensin receptors and angiotensin I converting enzyme during angiogenesis in the rat subcutaneous sponge granuloma. Br J Pharmacol1997; 120: 1302–1311.
29. Le Noble FAC, Hekking JWM, Van Straaten HWM, Slaaf DW, Struyker Boudier HA. Angiotensin II stimulates angiogenesis in the chorio-allantoic membrane of the chick embryo. Eur J Pharmacol1991; 195: 305–306.
30. Silvestre JS, Tamarat R, Senbonmatsu T, Icchiki T, Ebrahimian T, Iglarz M, et al. Antiangiogenic effect of angiotensin II type

2 receptor in ischemiainduced angiogenesis in mice hindlimb. Circ Res 2002; 90: 1072–1079.

31. Abali H, Gullu IH, Engin H, Haznedaroglu IC, Erman M, Tekuzman G: Old antihypertensives as novel antineoplastics: angiotensin- I-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists. Medical Hypotheses 2002; 59:344-348.

32. Uemura H, Ishiguro H, Nakaigawa N, Nagashima Y, Miyoshi Y, Fujinami,et al. Angiotensin II receptor blocker shows antiproliferative activity in prostate cancer cells: A possibility of tyrosine kinase inhibitor of growth factor. Molecular Cancer Therapeutics 2003; 2:1139-1147.

33. Tucker CE, Chen LS, Judkins MB, Farmer JA, Gill SC, Drolet DW. Detection and plasma pharmacokinetics of an anti-vascular endothelial growth factor oligonucleotide-aptamer (NX1838) in rhesus monkeys. Journal of Chromatography B 1999; 732 Suppl1:203-212.

34. Yoshiji H, Yoshii J, Ikenaka Y, Noguchi R, Yanase K, Tsujinoue H, et al. Suppression of the renin-angiotensin system attenuates vascular endothelial growth factor-mediated tumor development and angiogenesis in murine hepatocellular carcinoma cells. Int J Oncol 2002; 20:1227-1231.

35. Yoshiji H, Kuriyama S, Kawata M, Yoshii J, Ikenaka Y, Noguchi R, et al. The angiotensin-I-converting enzyme inhibitor perindopril suppresses tumor growth and angiogenesis: Possible role of the vascular endothelial growth factor. Clinical Cancer Research 2001; 7:1073-1078

36. Lever AF, Hole DJ, Gillis CR. Do inhibitors of angiotensin- I-converting enzyme protect against risk of cancer? Lancet 1998; 352 Suppl 9123:179-84.

37. Lang L. ACE inhibitors may reduce esophageal cancer incidence. Gastroenterology 2006; 131Suppl 2:343-4.

38. Fujita M, Hayashi I, Yamashina S. Blockade of angiotensin AT1a receptor signaling reduces tumor growth, angiogenesis and metastasis. Biochem Biophys Res Commun 2002; 294 Suppl 2:441-7.

39. Neo JH, Malcontenti Wilson C, Muralidharan V. Effect of ACE inhibitors and angiotensin II receptor antagonists in a mouse model of colorectal cancer liver metastases. J Gastroenterol Hepatol 2007; 22Suppl 4:577-84.

40. Lever AF, Hole DJ, Gillis CR, McCallum IR, McInnes GT, MacKinnon PL,et al. Do inhibitors of angiotensin-1-converting enzyme protect against risk of cancer? Lancet 1998, 352:179-184.