RENIN ANGIOTENSIN SYSTEM AND MALIGNANCY: A MINI REVIEW

Jisha M. Lucca¹, Nathani Minaz ², Nazeer Ahamed ³

¹Asst. Professor. Department of Pharmacy Practice, Bharat Institute of Technology- Pharmacy, Hyderabad, AP, India
²Asst. Professor. Department of Pharmacology, Bharat Institute of Technology- Pharmacy, Hyderabad, AP, India
³Asst. Professor. Department of Pharmacology, Vignan institute of pharmaceutical sciences, Hyderabad, AP, India

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 renin angiotensin system and malignancy. The renin–angiotensin system is usually associated with its systemic action on cardiovascular homeostasis. 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. 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. In rat and mouse, two AT1 subtypes have been cloned and characterized; they are termed AT1A and AT1B. 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. 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. 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. 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. 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 and in vivo. Increasing evidence supports a role of AT2 particularly in the regulation of growth, differentiation, and regeneration of neuronal tissue. The over expression of the vasoconstrictor AT1 was reported in association with human cancers of the breast, pancreas, kidney, squamous cell carcinoma, keratoacanthoma, larynx, adrenal gland, and lung. AT2 has been identified as...
expressed in preference to AT1 in only on colorectal cancer. 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. Further, numerous studies have shown antitumor and antiangiogenic effects of Ang II via Ang II type 2 receptor (AT2R), in opposition to actions of this peptide via the AT1R. 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.

**Mechanism for Antiangiogenic Effect of AT**

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. 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. This confirms earlier reports that ANG II stimulates angiogenesis in the chick embryo model. Silvestre et al. 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). 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. 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. 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. 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. 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. 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. 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. Candesartan was reported to reduce tumour related angiogenesis and the number of lung metastases in a murine lung cancer model. 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. 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. 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 antiangiogenesis 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


