Hypertension, cancer and angiogenesis: Relevant epidemiological and pharmacological aspects

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ABSTRACT

Hypertension and cancer are two leading diseases in the world. Often they coexist in patients. They share some common predisposing factors e.g., ageing, obesity, alcohol consumption and smoking habit. Abnormal angiogenesis (i.e. the formation of new blood vessels from an existing vasculature) is a common pathological feature, and some pro-angiogenic factors e.g., vascular endothelial growth factor, basic fibroblast growth factor, tumor necrosis factor–alpha and few interleukins are common mediators in both the conditions. Among these, the most important is vascular endothelial growth factor, a specific mitogen for vascular endothelium. It increases vascular permeability and induces proteolytic enzymes that are necessary for vascular remodeling. Monocyte/macrophages also have been shown to play a role in angiogenesis by releasing some of the above mediators. Angiogenesis is essential for the growth and metastasis of solid tumors. The essence of impaired angiogenesis (despite high level of angiogenic factors), probably due to signaling defects in the endothelium in hypertension, is not clearly understood. Some anticancer drugs e.g., taxanes, vinblastine, temozolomide and doxorubicin have antiangiogenic activity. Nevertheless, several classes of specific antiangiogenic agents are being evaluated for their anticancer effects and are emerging as new drugs for cancer treatment. COX-2 inhibitors (e.g., celecoxib and rofecoxib), neovastat, thalidomide analogues and some cytokine inhibitors also inhibit angiogenesis. Although certain antihypertensives are found to have antiangiogenic properties, some show pro-angiogenic activity. Also, a number of epidemiological studies have found an association between the use of antihypertensive drugs and risk of cancer. However, a better understanding of common cell biology and the relationship between hypertension and malignancy may be helpful in elucidating more preventive and therapeutic avenues to manage hypertension and cancer.

KEY WORDS: Antihypertensive drugs, macrophages, new blood vessel, tumors

Introduction

Hypertension is the most common cardiovascular disease and a major public health problem in both developed and developing countries. Hypertension is a major risk factor for stroke, coronary heart disease, cardiac failure and renal failure. Prevention and treatment of hypertension have been shown to reduce morbidity and mortality substantially.

Epidemiological evidence from prospective studies points to the possibility that there may be an association between the pathogenesis of hypertension and cancer. Many epidemiological factors and pathophysiological pathways are quite similar in two distinct disorders. Phaeochromocytoma, a rare tumor of the adrenal medulla is associated with hypertension. The incidence of both hypertension and cancer increases with the aging process and interestingly, some other risk factors are common. Obesity is responsible for hypertension and some forms of cancer. Similarly, alcohol consumption and smoking have a contributing role in blood pressure elevation and malignancy.

Worldwide, in the year 2000, approximately 56 million deaths occurred and non-communicable diseases accounted for 58% of the total number of deaths. Cancer accounted for over 7 million deaths (13% of total mortality and 22% of non-communicable disease mortality) worldwide in 2000, which was second to cardiovascular diseases (29% of total). Lung cancer was the leading cause of cancer deaths in the world, accounting for 17% of total cancer mortality. Lung cancer was also the most common cancer in the world in 2000, accounting for 13% of the total cancer incidence, followed by cancers of the colon and rectum, breast, stomach and liver. However, it is interesting to note that the majority of cancer patients have coexistent diseases. With more than 50% of the cancer patients reporting cardiovascular disorders including hypertension, co-morbidity is substantial.
Possible mediators linking hypertension and cancer

Nitric oxide (NO) has an important pathophysiological role in both hypertension and cancer. NO, in several biological processes and diseases, enables or enhances angiogenesis. Angiogenic growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) induce NO and require NO to elicit an effect. Further, NO modifies the release of cytokines from macrophages. Moreover, there is clear evidence of abnormalities in pulmonary NO levels of patients with lung cancer and primary pulmonary hypertension. NO-generating enzyme, the endothelial nitric oxide synthase (eNOS), is expressed in vascular endothelium, airway epithelium, and certain other cell types. The eNOS is an important component of vascular homeostasis and is activated by bradykinin.

The second mediator that may link hypertension and cancer is the renin-angiotensin system. Renin releases angiotensin I from angiotensinogen which subsequently gets converted to the biologically active angiotensin II by the angiotensin-converting enzyme (ACE). Angiotensin II acts on both the peripheral blood vessels and the central nervous system to increase blood pressure. In the central nervous system, rostral ventrolateral medulla has a large quantity of angiotensin-type 1 (AT1) receptors and angiotensin II binds to these receptors to exert its activity. Low-density lipoprotein cholesterol (LDL-C) has been demonstrated to upregulate the AT1 receptor, leading to increases in blood pressure. The role of the renin-angiotensin system in tumor angiogenesis is little understood. Both angiotensin II and AT1 receptors have been shown to stimulate angiogenesis. Angiotensin II induces VEGF, thereby playing an important role in VEGF-mediated tumor development and angiogenesis. Similarly, the AT1 receptor pathway supports tumor-associated macrophage infiltration, which results in enhanced tissue VEGF protein levels, angiogenesis and growth of tumor cells.

Epidemiological association between cancer and hypertension

Several studies have shown a relationship between hypertension and an increased cancer risk. High blood pressure is associated with increased risk of lung cancer in male hypertensive smokers. However, the studies were unable to qualify hypertension per se as an independent risk factor. An increased risk of breast cancer has been seen in hypertensive women and men. Also, the prevalence of dyslipidemia/hypercholesterolemia was higher in breast cancer patients. Amongst gynecological cancers, patients with endometrial cancer frequently have a history of hypertension. Similarly, steroid hormone dependent tumors i.e., prostate cancer and fast-growing benign hypertrophy of the prostate are associated with high systolic and diastolic blood pressures. Further, several studies have demonstrated that hypertension was associated with renal and colorectal neoplasia. Moreover, it has been observed that hypertension was associated with an increased risk of mortality from cancer and the overall survival was decreased by hypertension. Whether the coexistence of cancer and hypertension is a mere association or bears a real cause and effect relation, needs to be explored.

Factors influencing angiogenesis in hypertension and cancer

Angiogenesis is a prominent feature of cancer and its abnormality appears to play an important role in hypertension. Different important pro-angiogenic factors have been shown to be associated with hypertension. Compared with healthy controls, patients with hypertension have elevated plasma levels of VEGF. Also, VEGF protein expression was much higher in hypertensive than in normal rats. Similarly, many studies have observed an increase in the plasma levels of basic fibroblast growth factor (bFGF) and tumor necrosis factor-alpha (TNFα) among hypertensive patients. Moreover, after stimulation with angiotensin II, the secretion of interleukin-1 beta (IL-1 beta) by peripheral blood monocytes was shown to be increased significantly in hypertensive patients than healthy individuals. Several studies have demonstrated that the plasma interleukin-6 (IL-6) concentration was positively associated with hypertension. IL-6 is a multifunctional cytokine produced by macrophages, T-cells, B-cells, endothelial cells and tumor cells. IL-6 is able to promote tumor growth by upregulating antiapoptotic and angiogenic proteins in tumor cells. On the other hand, hypertension activates endothelial cells to increase the expression of IL-6, IL-8 and TNFα and induces neutrophil and monocyte adhesion and migration. Also, inflammatory markers of monocyte-endothelial cell interaction are elevated in hypertensives in comparison to normotensives.

Studies over the past 30 years have established that the development of new capillaries from an existing vascular network (angiogenesis) is an essential component for the growth of primary and metastatic solid tumors. Malignant tumors do not grow beyond 2-3 cubic mm in size unless they stimulate the formation of new blood vessels and thus provide a route for the increased inflow of nutrients and oxygen, and outflow of waste products. Tumor angiogenesis also provides an essential exit route for metastasizing tumor cells from the tumor to the blood stream. Angiogenesis is a complex, multistep process driven by many local signals within the tumor. Both pro-angiogenic and antiangiogenic factors secreted by the tumor, inflammatory and stromal cells play an important role in the regulation of neovascularization (Table 1). Amongst the most important of these is VEGF a specific mitogen for endothelium, which increases vascular permeability and induces proteolytic enzymes necessary for vascular remodeling. The low oxygen tension (hypoxia) present in the tumors is known to upregulate the expression of VEGF by tumor cells. Human macrophages also respond to hypoxia by increasing their release of VEGF in vitro. Moreover, macrophages are accumulated in higher numbers in poorly vascularized than highly vascularized areas of tumors. Therefore, the microenvironmental hypoxia that arises as a consequence of the development of a solid tumor also acts to promote tumor growth. Apart from inducing the expression of key factors of the angiogenic signaling cascades, hypoxia at the cellular level mediates the infiltration and accumulation of tumor-associated macrophages within avascular tumor regions. Complex interactions between tumor cell and macrophage hypoxia-regulated gene products and their associated pathways form the basis for the promotion of tumorigenesis and malignant progression.
Macrophages are supposed to play a key role in tumor angiogenesis. By release of VEGF, bFGF, transforming growth factor-alpha (TGF-alpha), IL-1, IL-6, IL-8 and TNF-α, activated macrophages have the capability to influence each phase of the angiogenic process, such as alterations of the local extracellular matrix and stimulation of vascular endothelial cells.

The tumor-infiltrating macrophage density correlates significantly and positively with intratumor microvessel counts and negatively with patients' survival. Quantification of microvessel density in the tumor specimen correlates with either metastasis or recurrence in many malignancies such as breast and lung cancer. Several studies have shown that the number of infiltrating macrophages were significantly associated with VEGF expression. On the other hand, VEGF has also been found to stimulate migration in macrophages. Thus, VEGF expression may be an important factor in the recruitment of tumor-associated macrophages. Further, some recent studies showed an association between the mutation of p53 protein and VEGF expression. It appears that VEGF is a major regulator of angiogenesis and vasculogenesis.

Antiangiogenic drugs

Angiogenesis begins with local degradation of the basement membrane-surrounding stroma by the endothelial cells in the direction of the angiogenic stimulus (Figure 1). It has already been mentioned that endothelial invasion is regulated by different autocrine and paracrine factors. Malignant invasion and physiological invasion share some common gene products and signaling cascades. Understanding the difference in gene expression in the development of the pro-angiogenic and invasive phenotype is an important step towards therapeutic targeting. Nevertheless, certain chemotherapeutic agents have potent antiangiogenic properties, which may be a part of their antitumor activity. Among taxanes, paclitaxel (taxol) and docetaxel (taxotere) have antiangiogenic activity. However, docetaxel appears to be more potent at inhibiting angiogenesis. Similarly, anticancer drugs such as vinblastine and temozolomide and doxorubicin are capable of inhibiting angiogenesis. On the other hand, antiangiogenic therapy using angiogenesis inhibitors is a relatively new and promising area of cancer treatment that specifically inhibits new blood vessel formation within the tumor. Physiologically, angiogenesis occurs during embryogenesis, wound healing and reproductive functions in adults. The architecture of tumor vessels is fundamentally different from that found in healthy tissues. Tumor vessels are usually irregular, heterogeneous, leaky, and poorly associated with stromal cells. Endothelial cells in tumor vessels are also disorganized and express imbalanced surface molecules. In animal tumor models, several angiogenesis inhibitors seem to inhibit specifically tumor angiogenesis without having obvious effects on the normal vasculature. More than 60 angiogenesis inhibitors are being evaluated for their anticancer effects in patients. Several classes of angiogenesis inhibitors that target different steps involved in angiogenesis include:

1. Drugs in...
Inhibiting matrix breakdown, the matrix metalloproteinase inhibitors, such as matrinastat, prinomastat and neovastat. (2) Drugs that block endothelial cell signaling via VEGF and its receptor like anti-VEGF antibodies. (3) Drugs that are similar to endogenous inhibitors of angiogenesis including endostatin, angiotatin, interferons and IL-12. (4) Thalidomide and its analogs have been shown to inhibit growth factor-induced neovessel formation. Moreover, (5) drugs such as celecoxib, rofecoxib, squalemine, fumagillin analog, and those targeting the integrins are also being evaluated as angiogenesis inhibitors.

Non-steroidal antiinflammatory drugs (NSAIDs), particularly selective cyclooxygenase-2 (COX-2) inhibitors such as celecoxib or rofecoxib have been shown to inhibit angiogenesis.\(^\text{60,61}\) COX-2 catalyzes the synthesis of prostanoids from arachidonic acid and there is evidence that it may promote tumor angiogenesis.\(^\text{60}\) COX-2 is upregulated in cancer cells, adjacent stromal cells and angiogenic endothelial cells during tumor progression.\(^\text{62}\) There is enough preclinical evidence that strongly supports the potential role of COX-2 inhibitors for the prevention and treatment of cancer.\(^\text{63}\) On the other hand, neovastat is another promising antiangiogenic drug purified from shark cartilage.\(^\text{63}\) The drug is effective after oral administration and induces endothelial cell apoptosis, inhibits matrix metalloproteinase activities and VEGF-mediated signaling pathways.\(^\text{64}\) Recently, it has been observed that a number of thalidomide analogs act as antimalignant drugs due to their T-cell co-stimulatory, antiangiogenic and antiinflammatory effects. These thalidomide analogs are known as immunomodulatory drugs and include revimid and actimid. Further, the other class of analogs termed as selective cytokine inhibitory drugs (SelCIDs) are phosphodiesterase 4 inhibitors. They do not stimulate T-cells. These analogs have been evaluated for their ability to inhibit tumor angiogenesis, vascularity and growth.\(^\text{65,66}\)

**Antihypertensive agents and angiogenesis**

Interestingly, bradykinin facilitates growth in many cancers by increasing tissue permeability and stimulating angiogenesis. Certain peptide and non-peptide bradykinin antagonists show potential anticancer properties by inhibiting angiogenesis (VEGF-mediated) and membrane metalloproteinase activity (MMP-2 and 9).\(^\text{67}\) It is well known that bradykinin is an important component of physiological blood pressure lowering system. Several antihypertensive drugs have effects on the process of angiogenesis.\(^\text{68}\) In general, drugs such as atenolol, diltiazem and enalapril do not affect \textit{in vitro} angiogenesis in cells within therapeutic ranges.\(^\text{69}\) On the other hand, drugs like mibebradil\(^\text{70}\) (calcium channel blocker) and terazosin\(^\text{71}\) (α1-blocker) show direct antiangiogenic activity. Similarly, angiotensin-converting enzyme (ACE) inhibitors such as captopril and perindopril have been shown to inhibit angiogenesis.\(^\text{72,73}\) Perindopril, which was shown to be a potent inhibitor of the growth of hepato cell carcinoma and angiogenesis, also suppresses VEGF at clinically relevant doses.\(^\text{74}\) On the contrary, it has been observed that the very low dose combination of perindopril and indapamide (a non-thiazide sulfonyl diuretic) induces neovascularization.\(^\text{75}\) Similarly, ACE inhibitor quinaprilat, an active metabolite of quinapril, promotes angiogenesis.\(^\text{75}\) Moreover, studies have recorded that angiogenesis was induced by administration of the α1-blocker prazosin\(^\text{76}\) and calcium channel blocker amlodipine.\(^\text{77}\) An increased concentration of VEGF was found in relation to the duration of prazosin treatment.\(^\text{75}\)

**Angiotensin II and neovascularization**

The formation of new blood vessels is a necessary physiological process in embryonic development and in repair mechanisms such as wound healing, tissue repair following ischemia and cyclical changes in the endometrium during the menstrual cycle.\(^\text{78}\) On the other hand, lack of blood vessel growth leads to many pathological conditions such as bowel atresia, unilateral facial atrophy, peptic ulcers, ischemic heart disease and peripheral vascular disease.\(^\text{79,78}\) Cardiovascular researchers have been exploring the feasibility of enhancing angiogenesis and thereby collateral vessel formation in patients with chronic ischemia of the myocardium or lower limb, by increasing the local concentrations of angiogenic growth factors either by giving recombinant protein or by gene transfer, or by administering endothelial progenitor cells that synthesize a cocktail of growth factors for angiogenesis.\(^\text{80}\)

By a complex mechanism, the renin-angiotensin system is involved in preserving the blood supply to organs in order to maintain normal cellular functions.\(^\text{81}\) Experimental evidence also indicates that angiotensin II tends to restore blood flow to the ischemic tissues and plays an important role in angiogenesis and thereby in maintaining tissue perfusion during sustained ischemia.\(^\text{81,82}\) Angiotensin II, the main effector peptide of the renin-angiotensin system, is implicated in the development of hypertension and exerts its actions through AT1 and AT2 receptors.\(^\text{83}\) Several investigators have demonstrated the positive role of angiotensin II and AT1 receptors in tumor angiogenesis.\(^\text{84,81,85}\) and the antiangiogenic effects of ACE inhibitors and AT1 receptor antagonists.\(^\text{86,82,73}\) On the other hand, some of the ACE inhibitors reportedly promote angiogenesis by slowing down bradykinin degradation and an obscure differential effect on the expression of AT receptors.\(^\text{81,84}\) Interestingly, many researchers have suggested that hypertension might influence cancer through vasoactive chemicals like angiotensin II.\(^\text{85,86}\) Moreover, inhibition of tumor growth and angiogenesis by ACE inhibitors\(^\text{87,88}\) indicates the role of angiotensin II as an angiogenesis promoting factor and its probable influence in the pathological process of cancer. Impaired angiogenesis may be due to some inherent problem of endothelial cells (signaling defect), which leads to defective response to a high level of pro-angiogenic factors in hypertension.\(^\text{78,89,90}\) and probably, high levels of these factors promote cancers as discussed earlier. In spite of a considerable number of studies over the past several years, the association between hypertension and the risk of cancer remains obscure.\(^\text{3,85,86,91}\) Similarly, several aspects of the relationship between hypertension and angiogenesis are controversial.\(^\text{27,78}\)

**Antihypertensive drugs and cancer**

Interestingly, antihypertensive treatment may promote cancer through unknown mechanisms.\(^\text{92}\) Analysis of various epidemiological, cohort and randomized studies of antihypertensive drugs shows that long-term use of some antihyper-
tensive drugs while preventing cardiovascular complications has been associated with increased risk of cancer. The most convincing evidence exists for the association between the use of diuretics and renal cancer. A recent study has shown that the use of immediate-release calcium channel blockers, thiazide diuretics, and potassium-sparing diuretics were associated with increased risk of breast carcinoma. Reserpine has been implicated in the development of breast cancer. Another study has documented higher mortality from lymphatic and hematopoietic cancers in drug-treated hypertensive women as compared to normal women, and higher mortality from cancers of the uterus, cervix and ovary in those who were on antihypertensive treatment. Furthermore, several calcium channel blockers have been shown to block apoptosis in animal and in vitro studies. On the basis of these observations, it has been hypothesized that calcium antagonists may function as cancer promoters and that they might cause cancer in humans. However, conflicting reports on the use of calcium channel blockers and the occurrence of cancer have been observed. Similar conflicting results were observed in case of atenolol and ACE inhibitors with reference to the risk of cancer. Overall, the findings of different studies on the association between antihypertensive medications and the development of cancer are contradictory.

Conclusions

A substantial number of cancer patients have cardiovascular co-morbidity, particularly hypertension. These two distinct diseases, i.e., cancer and hypertension, can share some common pathophysiological mediators, and through these, hypertension might influence the promotion of tumorgenesis and malignant progression. Several studies documented an association between hypertension and the risk of cancer. This observation is somewhat clearer in the case of lung cancer, which is the most common cancer in the world including America and Europe. An increased risk of lung cancer has been noticed among hypertensive smokers. However, the process of neovascularization or angiogenesis is a phenomenon that plays a significant role in both hypertension and cancer. Different important pro-angiogenic factors such as VEGF, bFGF, TNF-alpha, TGF-alpha, IL-1, IL-6, IL-8, etc. are secreted by tumor, inflammatory and stromal cells. The level of angiogenic factors is high in hypertension. Among inflammatory cells, monocytes/macrophages demonstrate wide heterogeneity in biological function and have an essential role in angiogenesis. Macrophages are terminally differentiated cells that produce a number of potent angiogenic cytokines and growth factors, and influence various stages of angiogenesis. Recently, some studies have demonstrated that the renin-angiotensin system plays an important role in VEGF-mediated angiogenesis. In experimental cancer therapy, inhibition of angiogenesis has become a major goal to block the tumor growth. This therapeutic approach requires a precise knowledge of angiogenesis. In this context, more studies at the basic biological level may improve our understanding of the relationship between hypertension and malignancy.

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