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Review Article

Immunological and Inflammatory may Participate in the Development and Pathogenesis of Hypertension

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Abstract

Hypertension is a powerful risk factor for cardiovascular disease and frequently occurs in conjunction with obesity and the metabolic syndrome. Recent research into the underlying pathophysiologic processes common to these entities has uncovered the role of a heightened inflammatory state signified by a host of circulating biocytokines. Recent data however, have suggested that components of the innate and adaptive immune system also contribute to hypertension. Traditionally, atherosclerosis has been considered an inflammatory disease, however increasing evidence suggests that inflammation also contributes to hypertension, and if efforts are taken to block inflammation, the end-organ damage and severity of blood pressure elevation can be reduced. Surprisingly, thymus-derived lymphocytes (T cells) seem to be involved in hypertension, indicating that the adaptive immune system might contribute to this disease.

INTRODUCTION

As we know Hypertension is common disease and a powerful risk factor for cardiovascular disease. The pathophysiologic mechanism is sophistication and unclear. Recent research into the underlying pathophysiologic processes common to these entities has uncovered the role of a heightened inflammatory state signified by a host of circulating biocytokines, which demonstrate that Immunological and Inflammatory may participate in the development and pathogenesis of hypertension. However wee can not find anything about the inflammation or immunological aspect discussed. Recently many experiments have show that inflammation and immunity in animal studies but rare proof indicated inflammation contributes the human hypertension. Traditionally, atherosclerosis has been considered an inflammatory disease, however more and more studies suggests that inflammation may contributes to hypertension, as a result, if inflammation is blocked, the end-organ damage and severity of blood pressure elevation can be reduced. Surprisingly, thymus-derived lymphocytes (T cells) are involved in hypertension, indicating that adaptive immune system might contribute to this disease. But the exact manner by which T cells and other inflammatory cells contribute to hypertension is not yet to be understood.

IMMUNE SYSTEM

The innate immune is the first line of defense against pathogens; components include epithelial cells, which prevent pathogen entry, professional phagocytes (neutrophils, macrophages), the complement system, and pattern recognition receptors. Adaptive immunity is antigen-presenting cells (APCs) in peripheral tissues take up foreign proteins, such as those of bacteria and viruses, and processes them into short peptides that are presented in the context of a major histocompatibility complex (MHC). Activation of CD4+ lymphocytes is predominantly mediated by dendritic cells, which process antigens in phagosomes and present the resultant antigenic peptides within MHC II. Dendritic cells then migrate to secondary lymphoid organs, including the spleen and lymph nodes, where they seek a T cell that has a T cell receptor that recognizes the antigenic peptide. The interaction of the MHC with the T cell receptor occurs at a region termed the "immunologic synapse." Numerous other ligands and receptors interact at this site, and these promote a coordinated signal that affects both the APC and the T cell. An important additional interaction that occurs at this site, referred to as "co stimulation," involves B7 ligands on the APC (CD80 and CD86) with CD28 on the T cell. As we know there is actually enormous interplay between the innate and adaptive immunity. Nitric oxide and ROS

can modulate T cell function and survival. Cytokines produced by macrophages, dendritic cells, and other cells in the inflammatory milieu can influence T cell polarization and alter T cell function. Molecules such as nitric oxide, superoxide, cytokines, and ligands for TLRs regulate expression of vascular adhesion molecules and chemokines that promote entry of T cells into target tissues.

ROLE OF INFLAMMATION/IMMUNITY IN HYPERTENSION

Inflammation plays a key role in the pathogenesis and progression of atherosclerosis, cardiovascular disease and hypertension [1–4]. Tissue expression and plasma concentrations of inflammatory markers and mediators are increased in patients with cardiovascular disease [5]. Those molecules include CRP [5], adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) [5–8], chemokine's such as monocyte chemo attractant protein-1 (MCP-1), as well as anti-fibrinolytic agents such as plasminogen activator inhibitor-1 (PAI-1). Up regulation of inflammatory mediators in tissues, such as nuclear factor-kB (NF-kB), activator protein-1 (AP-1), the adhesion molecules VCAM-1, ICAM-1, platelet endothelial cell adhesion molecule and tissue factor [9], has been demonstrated in experimental hypertension.

Svendson showed that the delayed phase of DOCA salt hypertension was blunted in thymectomized animals [10]. Grollman et al also showed that immunosuppression attenuates hypertension in rats with partial renal infarction [11]. Pre-eclampsia is associated with an increase in lymphocyte markers and the cytokine profile of natural killer lymphocytes in the uterus [12,13]. Several studies focused on immune perturbations in the spontaneously hypertensive rats (SHR) suggested that T cell function is paradoxically depressed in this commonly-studied model of genetic hypertension. [14,15] In recent studies have found that RAG-1−/− mice, which lack both T and B cells, have very blunted hypertensive responses to prolonged angiotensin II infusion or DOCA-salt challenge. RAG-1−/− mice were also protected from the increase of vascular superoxide production and from loss of endothelium-dependent vasodilatation that generally accompany angiotensin II infusion. Following adoptive transfer of T cells, but not of B cells, hypertension caused by angiotensin II was completely restored to levels observed in wild-type mice [16]. Crowley et al have examined the hypertensive response in mice that have severe combined immunodeficiency [17]. These animals have a genetic abnormality leading to abnormal somatic recombination, such that they do not develop T or B cells, in a manner similar to RAG-1−/− mice. Crowley et al confirmed that T cells are essential for full development of angiotensin II–induced hypertension, and showed that these animals have reduced left ventricular hypertrophy, reduced cardiac fibrosis, and reduced albuminuria following angiotensin II administration. From recent studies we can say that chronic angiotensin II infusion increases the percent of cells CD69 and CCR5 positive and CD44 T cells in the circulation. These are markers of activated, effector T cells. Angiotensin II also markedly increased vascular levels of RANTES. Thus, like many inflammatory stimuli, hypertension has a dual effect: one is to promote T cell activation, and the second is to increase chemokine and adhesion molecule expression in target tissues to promote tissue entry of activated inflammatory cells. In keeping with this, hypertension also causes a marked infiltration of CCR5+ cells into perivascular fat [18]. Several studies also demonstrated renal tubule interstitial infiltration of activated macrophages and T lymphocytes in various animal models of HTN [19-21,23-25], These findings show the association of HTN with inflammation. The infiltrating immune cells have been shown to produce superoxide and express angiotensin II, events that can contribute to oxidative stress and HTN [19,20]. This assumption has supported by the reducing the inflammatory infiltrate result in amelioration of HTN [23-26]. It is of note that the activated immune cells release large quantities of ROS which promotes regional oxidative stress. Conversely, oxidative stress promotes inflammation by activating the redox-sensitive transcription factor, nuclear factor-kappa B (NF-kappa B) which, in turn, triggers generation of proinflammatory cytokines and chemokines, and hence, inflammation. Hypertension stimulates lymphocytic infiltration in the kidney, and immunosuppressive therapy prevents this and reduces renal damage while lowering blood pressure [19,23], but not all [27,28].There is increasing evidence supporting the role of renal tubulointerstitial and vascular inflammation in the pathogenesis of HTN [29,30]. In fact, renal tubulointerstitial infiltration of T lymphocytes and macrophages has been shown in essentially all animal models of hereditary and acquired HTN. Renal tubulointerstitial inflammation is accompanied by activation of NF-kappa B, [31,22,32] which is the general transcriptional factor for many pro inflammatory cytokines, chemokine's, and adhesion molecules. In addition, several studies have demonstrated activation of circulating leukocytes in hypertensive humans and animals. [33-41] The causal role of inflammation in the pathogenesis of HTN is supported by a number of animal studies that have shown amelioration of HTN with interventions aimed at blocking inflammation including the use of NF-kappa B activation inhibitor,[42,43] and the immunosuppressive drug, mycophenolate mofetil [26,43,44].

T LYMPHOCYTES IN PATHOGENESIS OF HYPERTENSION

Recent data suggest that subsets of T lymphocytes, both effector T cells such as T-helper Th1 (interferon-γ-producing) and Th2 lymphocytes [that produce interleukin (IL)-4], as well as Th17 (that produce IL-17), and T suppressor lymphocytes including regulatory T cells (Treg), which express the transcription factor forkhead box P3 (Foxp3), play critical roles in the development of angiotensin II, deoxycorticosterone salt-sensitive and Dahl salt-sensitive hypertension, and in the progression of vascular remodeling. As well, recent evidence suggests that the inflammatory response involving T lymphocytes may be triggered by oxidative stress in nuclei of the brain and associate with blood pressure elevation. Viel et al studied rats harboring the Dahl salt-sensitive (SS) genome except for chromosome 2 of the Brown Norway strain (SSBN2) rats [45]. Chromosome 2 contains genes associated with both hypertension and inflammation and has quantitative trait loci for hypertension. Authors found that SSBN2 rats have reduced hypertension, fewer inflammatory cells in the aorta and less vascular hypertrophy than do Dahl SS rats. They also showed that the aorta of these animals has more aortic Treg cells as evidenced by an increase

in mRNA for FoxP3b compared with Dahl SS animals. IL-10 represents an important anti-inflammatory cytokine that both induces and is produced by Treg cells. Tregs of SSBN2 rats were found to produce more IL-10 than did Tregs from Dahl SS rats. The authors concluded that Tregs play an important role in mitigating both blood pressure elevation and end-organ damage in the SSBN2 animals. Witowski et al. provided support for the role of a non-TH1 cytokine in hypertension. The cytokine IL-17 a novel cytokine produced by TH17 cells, cytotoxic T cells, mast cells, neutrophils and natural killer T cells [46]. TH17 cells are thought to develop independently of the TH1 or TH2 lineages, and seem to both promote and in some cases inhibit inflammation [47,48]. Madhur et al. found that chronic angiotensin II infusion increased the percent of circulating TH17 cells by 2- to 3-fold and caused accumulation of vascular levels of IL17 [49]. The hypertension and vascular dysfunction caused by angiotensin II was reduced in IL-17−/− mice. Importantly, IL-17 has been shown to induce chemokines and adhesion molecules in tissues that promote tissue accumulation of other inflammatory cells. In keeping with this, authors found that vascular accumulation of leukocytes that accompanies angiotensin II-infusion was virtually eliminated in IL-17−/− mice. Hence IL-17 seems to be an important cytokine that participates in hypertension and purposed that T cells residing in the perivascular fat release cytokines such as IL-17, that diffuse to the adjacent vascular smooth muscle cells where they enhance superoxide production, reduce endothelium-dependent vasodilatation and promote vasoconstriction. It is quite likely that other cytokines, such as TNFα and IL-6 also contribute by creating a cytokine milieu that promotes hypertension.

Hypertension has variously been attributed to alterations of renal function, vascular function and altered CNS signaling. Several studies have linked the central nervous system to inflammation. The principal neurotransmitter released at the sympathetic nerve terminal is norepinephrine, which can both inhibit and stimulate T cell activation and proliferation [50]. Lymph nodes and the spleen are richly innervated with sympathetic nerves that terminate in T cell rich areas [51,52]. Norepinephrine stimulates naïve CD4+ lymphocytes cultured under *TH1*-promoting conditions to produce 3- to 4-fold more IFNγ than in nonstimulated cells [53]. The pre-existing state of the T cell seems to determine the ultimate effect of β-adrenergic activation. Structures in forebrain with multiple integrative roles in neuroendocrine control of the circulation are involved. Tissue surrounding the anteroventral region of the third cerebral ventricle (AV3V region) is involved physiologically in thirst, sodium homeostasis, osmoreception, secretion of vasopressin and natriuretic factor and sympathetic discharge to blood vessels. Destruction of this tissue prevents or reverses many forms of hypertension. In genetically based spontaneous hypertension, limbic structures such as the central nucleus of the amygdala rather than the AV3V region are the necessary neuroanatomic substrate. Recent evidence suggests that a circumventricular organ in brain stem, the area postrema, is also involved in the mediation of several forms of experimental hypertension. In renin- and nonrenin-dependent forms of renal hypertension, two major factors activate central mechanisms. First, direct central actions of angiotensin, acting through receptors in the subfornical organ and organum vasculosum of the lamina terminalis, increase sympathetic discharge and secretion of vasopressin through mechanisms integrated at the level of the AV3V region. Second, sensory systems originating in the kidney can activate increased sympathetic discharge through complex projection pathways involving forebrain systems. Mineralocorticoid hypertension appears to involve enhanced secretion of vasopressin and central vasopressinergic mechanisms also dependent on the AV3V region. Reciprocal connections between key central areas involved in control of arterial pressure provide the neuroanatomical basis for central nervous system participation inhypertension. Oxidative stress in the brain, the vasculature and the kidney clearly contribute to hypertension via mechanisms that are poorly clear to us. How these various systems are involved in T cell activation and how oxidative events contribute to T cell activation remain unclear. Recent study showed that oxidative stress in the circumventricular organs (CVO) of the brain, and in particular in the subfornical organ, likely participates in this process. These regions lack a well-formed blood brain barrier and are therefore affected by circulating signals like angiotensin II. Similar study by Davisson has shown that reactive oxygen species produced in neurons of the CVO contribute to hypertension, in part by promoting sympathetic outflow. Lob et al. produced mice in which loxP sites were placed on either side of the coding region of the extracellular superoxide dismutase (ecSOD or SOD3). This permitted deletion of SOD3 in adult animals by intracerebroventricular (ICV) injection of an adenovirus expressing Cre-recombinase (AdCre). Acute deletion of SOD3 caused an oxidative insult in the CVO, raised systemic blood pressure by 20 mmHg and markedly sensitized the mice to infusion of low-dose angiotensin II. More importantly, authers observed that this central manipulation caused an increase in the percent of T cells with an activated phenotype, and markedly increased the vascular inflammation associated with angiotensin II infusion. Analysis of heart rate and blood pressure variability indicated that deletion of SOD3 in the CVO markedly enhanced sympathetic outflow [54]. These data are in keeping with prior studies by Ganta et al, suggesting that sympathetic outflow can promote T cell activation [55].

CONCLUSION

A growing body of evidence suggests that Immunity and inflammation participates in the development and pathogenesis of hypertension. Hypertension may be considered a low-grade inflammatory disease. From this review we can have gross ideas for treatment of hypertension contrast to the traditional treatment methods.

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