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Novel Pathophysiological Mechanisms in Hypertension

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Abstract

Hypertension is the most common disease affecting humans and imparts a significant cardiovascular and renal risk to patients. Extensive research over the past few decades has enhanced our understanding of the underlying mechanisms in hypertension. However, in most instances, the cause of hypertension in a given patient continues to remain elusive. Nevertheless, achieving aggressive blood pressure goals significantly reduces cardiovascular morbidity and mortality, as demonstrated in the recently concluded SPRINT trial. Since a large proportion of patients still fail to achieve blood pressure goals, knowledge of novel pathophysiologic mechanisms and mechanism based treatment strategies is crucial. The following chapter will review the novel pathophysiological mechanisms in hypertension, with a focus on role of immunity, inflammation and vascular endothelial homeostasis. The therapeutic implications of these mechanisms will be discussed where applicable.

Keywords

Hypertension • Pathophysiology • Immune system • Neuro-inflammation • Bone marrow • RAAS • AT_2 receptor • Angiotensin- (1–7) • Mineralocorticoid receptor • VEGF • ADMA

1 Introduction

Hypertensive cardiovascular disease represents a complex spectrum of pathophysiological abnormalities associated with the biomarker of high blood pressure. Our understanding of the complex processes that lead to essential hypertension

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has significantly increased over the past few decades. Established pathophysiological mechanisms in essential hypertension include: heightened sympathetic nervous system activity (SNS), alterations in the renin-angiotensin-aldosterone (RAAS) system, excess of sodium-retaining hormones and vasoconstrictors and lack of vasodilators (such as prostacyclin, nitric oxide (NO), and natriuretic peptides), disturbances in the kallikrein–kinin system, abnormalities of resistance vessels and renal microvasculature, and increased vascular growth factor activity (James et al. 2014; Takamura et al. 1999; Davies 2008).

Despite numerous advancements in our understanding of the pathophysiological mechanisms and in treatment strategies however, hypertension continues to remain the most common disease in humans. Novel pathophysiologic mechanisms and mechanism based treatment strategies need to be urgently explored to improve blood pressure control and cardiovascular outcomes in hypertensive patients. The following review summarizes some the key pathophysiological mechanisms in hypertension that have been recently described. Novel insights into the role of the immune system, neuroinflammation and bone marrow in hypertension will be first discussed. Next, recent evidence describing the vasculo-protective effect of the RAAS pathway and the vaso-deleterious effect of the mineralocorticoid receptor will be addressed. Alterations in vascular homeostasis and nitric oxide pathways through vascular endothelial growth factor (VEGF) inhibitors and asymmetric dimethylarginine (ADMA) will be considered last (Kandavar et al. 2011; Calhoun et al. 2000). "Finally, the effect of vascular endothelial growth factor (VEGF) inhibitors and asymmetric dimethylarginine (ADMA) on vascular homeostasis and nitric oxide pathways will be considered."

2 Immune System

Initial evidence for the contribution of the immune system (IS) to hypertension came from studies that demonstrated that immunosuppression lowered blood pressure in rats with partial renal infarction (White and Grollman 1964). In later studies, Olsen noted that mononuclear cells in rats adhered to and infiltrated damaged endothelium in response to angiotensin (Ang)-II infusion (Olsen 1970). Furthermore, athymic mice displayed blunted hypertensive responses and subsequent treatment with anti-thymocyte serum and cyclophosphamide reduced blood pressure (Olsen 1970; Bendich et al. 1981). Altered antibody production was also noted in the spontaneously hypertensive rat (Dzielak 1991; Takeichi et al. 1988; Takeichi and Boone 1976; Purcell et al. 1993). After these early studies in the 1980s, the link between the IS and hypertension remained unexplored for more than two decades. However, with the advent of new molecular tools and genetically engineered animal models, the field of immunology has grown tremendously, offering investigators greater insight into the role of the immune cells, cytokines and cell trafficking in hypertension.

2.1 T-Cell

Knock-out mice lacking recombinant activating genes (RAG) 1 or 2 develop a diminished response to Ang-II or DOCA salt challenge (Guzik et al. 2007). Hypertension was associated with perivascular adipose tissue and adventitial aggregation of effector type T-cells in $RAG1^{-/-}$ mice. Hypertensive response was restored with an adoptive T-cell transfer into $RAG1^{-/-}$ mice. Blunted hypertensive response to stress and recovery following T-cell transfer was further noted in $RAG1^{-/-}$ mice (Guzik et al. 2007).

Severe combined immunodeficiency in mice prevents development of hypertension (Crowley et al. 2010). Reduced hypertension was similarly observed in Dahl-sensitive rats with RAG1 gene knockout (Mattson et al. 2013). Adoptive transfer of regulatory T lymphocyte (Tregs) that suppress innate and adaptive immune responses prevented Ang II-induced blood pressure elevation, vascular stiffness and inflammation (Barhoumi et al. 2011; Muller et al. 2002). Vasculo-protective effects of Tregs have been further demonstrated in aldosterone-induced vascular dysfunction and hypertension (Kasal et al.

2012). Mycophenolate mofetil, a T cell suppressing agent improved blood pressure and renal inflammation in several animal models (Bravo et al. 2007; Franco et al. 2007; Herrera et al. 2006). In a small study of hypertensive patients with rheumatoid arthritis and psoriasis, Mycophenolate reduced blood pressure (Herrera et al. 2006).

2.2 Innate Immunity

Macrophage colony stimulating factor knockout mice, deficient in macrophages and monocytes, exhibit minimal response to Ang-II infusion and unaltered endothelium dependent vasodilation (De Ciuceis et al. 2005). This animal model, known as the osteoporosis spontaneous mutation mice, are further resistant to DOCA-salt hypertension (Ko et al. 2007). Increased aortic monocytes/macrophages and inflammation (as inferred by vascular cell adhesion molecule-1, cyclooxygenase 2, and inducible nitric oxide synthase mRNA) develops in response to Ang-II. Using lysozyme M–targeting of the diphtheria toxin receptor to delete monocytes, Wenzel et al. preempted the vascular alterations and hypertension caused by Ang-II (Wenzel et al. 2011). Transferring monocytes to these mice restored hypertension in these mice.

2.3 Cytokines

Hypertension causes infiltration of effector T cells and monocytes/macrophages in the perivascular regions of both large arteries and arterioles and the kidneys (Olsen 1970; Guzik et al. 2007; Wenzel et al. 2011). Potent cytokines locally released by these cells cause deleterious effects on the vasculature and renal function: this contributes to sustained hypertension and end organ damage. The role of important cytokines in hypertension, namely: interleukin-17A (IL-17A), interleukin 6 (IL-6), and Interferon-γ (IFN- γ) are discussed below:

Interleukin 17 Production of IL-17A is increased in hypertensive patients and mice exposed to Ang-II (Madhur et al. 2010). Minimal hypertensive response and endothelial dysfunction in response to Ang-II was reported in IL-17A deficient mice. Increase in vascular superoxide production and infiltration with T cells was significantly reduced in IL-17A deficient mice. Elevated blood pressure in mice given IL-17A infusion is attributed to conformational changes in endothelial nitric oxide synthase (eNOS) and the resultant decrease in nitric oxide (NO) (Fleming et al. 2001; Piazza et al. 2014). Recently, Amador et al. found that treatment with spironolactone reversed the increase in circulating T_H17 cells and normalized IL-17A mRNA in the heart and kidney of rats with DOCA-salt hypertension (Amador et al. 2014). Antibody against IL-17A reduced blood pressure and collagen-1 levels in the heart and kidney (Amador et al. 2014). Further, collagen deposits and aortic stiffening were absent in IL-17A−/− mice in contrast to the marked collagen deposits and aortic stiffening in Ang-II and DOCA-salt–induced hypertension (Wu et al. 2014).

Interleukin 6 IL-6 is produced by various cells of the IS and has been found to contribute to hypertension. Higher levels of IL-6 seen in hypertensive patients are reversed by Ang-II-receptor blockade (Vázquez-Oliva et al. 2005). Treatment with spironolactone blocks angiotensin II mediated increase in IL-6 levels (Luther et al. 2006). Mice deficient in IL-6 have minimal increase in blood pressure in response to a high salt diet and angiotensin-II (Lee et al. 2006). Activity of epithelial sodium channel is enhanced by IL6 in cultured collecting duct cells (Li et al. 2010). Apart from these direct effects, IL-6 transforms regulatory CD4+T cells to IL-17 producing phenotype, further contributing to hypertension.

Interferon-γ IFN- γ promotes angiotensinogen expression in both hepatocytes and renal proximal tubular cells (Jain et al. 2006; Satou et al. 2012). Angiotensinogen is further converted into Ang-I and Ang-II (Kobori et al. 2007). Locally produced Ang-II acts through various sodium ion

transporters to increase sodium uptake and volume in the proximal and distal tubules. Kamat el al recently demonstrated perturbations in sodium transporters in IFN-γ deficient mice, thereby promoting natriuresis and sodium reabsorption (Kamat et al. 2015). Thus, in addition to modifying RAAS systems locally IFN-γ alters expression of renal sodium transporters thereby impacting the sodium and water balance.

2.4 Novel Mechanisms of T Cell Activation

Role of Isoketals Recent studies have revealed new mechanisms of T cell activation in hypertension, a phenomenon that was unexplained despite the large body of evidence supporting a role of the IS in hypertension (Kirabo et al. 2014). Upregulation of NADPH oxidase in dendritic cells promotes production of reactive oxygen species. Oxidation of arachidonic acid leads to formation of γ-ketoaldehydes or isoketals. Protein lysines and isoketals combine in dendritic cells to make immunogenic proteins that are then presented to T cells resulting in T cell activation and proliferation (Miyashita et al. 2014). Further, isoketals independently promote cytokine production in dendritic cells and T cells. Isoketal scavenger 2 hydroxybenzylamine halts dendritic cells from producing cytokines and T cell activation. Additionally, a blunted hypertensive response was noted in mice receiving dendritic cells from donors treated with 2 hydroxybenylamine (Kirabo et al. 2014; McMaster et al. 2015).

Toll-Like Receptors and Damage Associated Molecular Patterns Ubiquitously expressed in the immune cells and the cardiovascular system, toll-like receptors (TLRs) recognize and initiate inflammatory responses to dangerous molecules (Frantz et al. 2007; Matzinger 2002). Aside from pathogens, endogenous molecules produced following cellular injury or death (damage-associated molecular patterns (DAMPs)) also activate TLRs (Theodora Szasz 2013). Recent investigations have highlighted the inflammatory properties of mitochondrial DNA as a result of TLR activation (Oka et al. 2012; Zhang et al. 2010). TLRs promote vascular dysfunction, low-grade inflammation and release of pro-inflammatory cytokines, all contributing to hypertension (Bomfim et al. 2012; Liang et al. 2013; De Batista et al. 2014; Singh and Abboud 2014). Initial innate IS TLRs response to DAMPs may thus be a necessary precursor of the adaptive IS activation observed in hypertension (McCarthy et al. 2014). Low complexity of TLR signaling pathway and availability of specific inhibitors may lead to the development of novel anti-hypertensive drugs.

3 Neuro-Inflammation

The association between hypertension and inflammation in the brain is evident from studies in animal models of hypertension demonstrating elevated levels of cytokines such leukotriene-B, nuclear factor-κb, TNF-α, IL-1β, and IL-6 in the brain (Waki et al. 2013; Santisteban et al. 2015; Cardinale et al. 2012; Song et al. 2014). Angiotensin converting enzyme (ACE) and Ang-II upregulate neuronal inflammatory pathways (Marc and Llorens-Cortes 2011; Agarwal et al. 2013; Shi et al. 2014). Exposure of cardioregulatory forebrain structures to TNF-α, IL-1β heightens SNS activity and blood pressure while anti-inflammatory drugs pentoxyphylline and minocycline attenuate the development of hypertension (Xue et al. 2016; Wei et al. 2015; Sriramula et al. 2013).

Innate IS activation through microglial cells also promotes SNS activity, peripheral inflammation and hypertension (Masson et al. 2015; Shi et al. 2010). Under normal conditions, microglial cells act to promote immune homeostasis within the brain environment. Upon activation of microglia through pathological insults or alterations in homeostasis, there is an induction of centrally produced proinflammatory cytokines, thereby contributing neuro-inflammation, and consequently, hypertension (Agarwal et al. 2013; de Kloet et al. 2015). Inhibition of microglial activation attenuates SNS

activity, peripheral inflammation and hypertension (Santisteban et al. 2015; Shi et al. 2014).

4 Bone Marrow

The impact of peripheral and neuro-inflammation in hypertension has been described thus far. The relationship between the IS and the brain in hypertension was, however, poorly understood until recent investigations revealed a critical role of the bone marrow in regulating peripheral and neuro-inflammation in hypertension (Santisteban et al. 2015). As a site of inflammatory cell generation and convergence of CNS and IS, the BM was suggested as an ideal link between inflammatory system and hypertension. Indeed, the BM of spontaneously hypertensive rat had increased levels of inflammatory cells and cytokines, as well as migration of these cells into the hypothalamic paraventriuclar nucleus (Santisteban et al. 2015). Minocycline, through its anti-inflammatory effects, prevented both peripheral and neuro-inflammation, thereby attenuating hypertension (Santisteban et al. 2015).

SNS Effect on BM Hematopoietic stem and progenitor (HSPC) stem cell homeostasis is regulated by SNS via adrenergic nerve fibers that richly innervate the bone marrow. Central sympathetic outflow stimulates HSPC mobilization and release into circulation (Hanoun et al. 2015; Méndez-Ferrer et al. 2008). Multiple mechanisms contribute to this upregulation of HSPCs from the BM by sympathetic stimulation, including granulocyte-colony stimulating factor induced osteoblast suppression, modulation of the Wnt-B – catenin pathway, and substance P-mediated nociceptive signaling (Katayama et al. 2006; Spiegel et al. 2007; Amadesi et al. 2012). Ang-II increases HSPC proliferation in BM and inflammatory monocyte production in the spleen (Kim et al. 2016). Conversely, disruption of sympathetic tone impairs HSPC mobilization (Lucas et al. 2012).

SNS Effect on the Immune System Autonomic regulation of the IS seems to play an important role in hypertension (Scheiermann et al. 2013; Ganta 2005). Chronic Ang-induced hypertension animal models express inflammatory monocytes in BM, spleen and peripheral blood, contributing to hypertension (Santisteban et al. 2015; Swirski et al. 2009). Independent of the SNS effect on the BM, norepinephrine induces memory T cell production of cytokines in the vasculature and the kidneys (Marvar et al. 2010; Slota et al. 2015; Trott et al. 2014). Norepinephrine increases recruitment of immune cells from BM, while acetylcholine opposes this effect (Zubcevic et al. 2014). Lastly, renal denervation inhibits IS activation and preempts renal inflammation in Ang-II induced hypertension (Xiao et al. 2015).

Thus, a positive feedback loop is established, whereby neuro-inflammation contributes to sympathoexcitation, which then promotes activation of the IS and stem/progenitor cells in BM. In turn, this can exacerbate central inflammation generating a vicious proinflammatory cycle (Fig. 1) (Young and Davisson 2015). Extravasation of proinflammatory precursors from the BM to hypothalamic paraventricular nucleus causing neuro-inflammation in Ang-II–induced hypertension has been demonstrated (Santisteban et al. 2015; Spiegel et al. 2007). Mechanisms of extravasation of BM cells into the brain are currently unknown.

5 Vasculo-Protective RAAS Pathways

RAAS blockade generates alternate metabolites of Ang that can exert an anti-hypertensive effect. Vasculo-protective RAS pathways include Angiotensinase A-Ang III-Ang II type 2 (AT_2) receptor pathway and ACE 2-Ang-(1–7)-Mas receptor pathway (Te Riet et al. 2015).

5.1 AT_2 Receptor Pathway

Upregulation of AT_2 receptors counteracts the vaso-deleterious effects of angiotensin (AT_1) type 1 receptor. Mice deficient in AT_2 receptor exhibit increased blood pressure and baroreflex

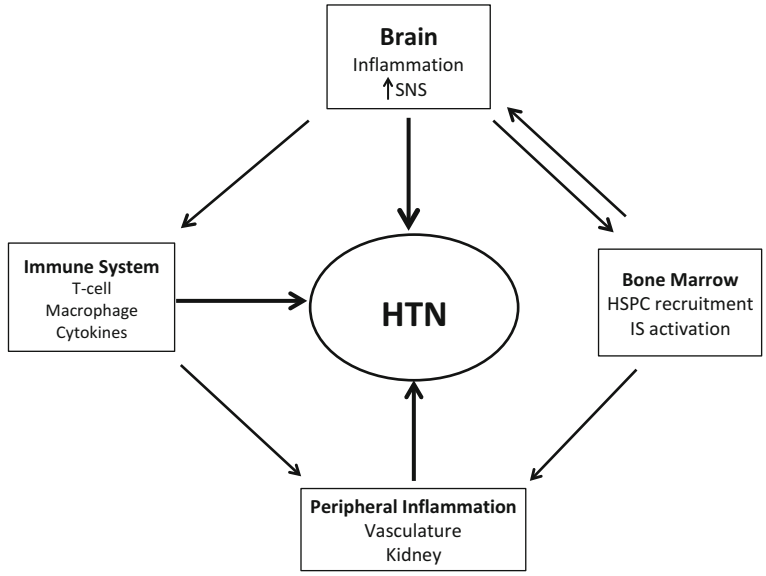

Fig. 1 Role of Immune system activation, brain and bone marrow in hypertension. Immune system activation via T cells, macrophages and various cytokines results in central and peripheral inflammation in the vasculature and kidney contributing to hypertension. Neuro-inflammation from hypertensive stimuli promotes sympathetic nervous system (SNS) activity causing hypertension. SNS activity in bone marrow increases recruitment and release of hematopoietic stem cell progenitors (HSPC) and cytokines, furthering the pro-inflammatory state

sensitivity, and decreased pressure-natriuresis and AT_1 receptor expression (Gross et al. 2004; Tanaka et al. 1999; Gembardt et al. 2008). Overexpression of AT_2 receptor reverses these effects (Tsutsumi et al. 1999). Four AT_2 agonist molecules are currently being developed for clinical use in hypertension namely: peptidergic agonists β-Tyr4-Ang II, β-Ile5-Ang II and LP2-3 and the non-peptide agonist Compound 21 (C21). AT_2 receptor mediated aortic vasodilation was reported in mice treated with peptidergic agonists (Jones et al. 2011; Wagenaar et al. 2013). Interestingly, vasodilatory effects of AT_2 receptor are appreciated most on a background of partial AT_1 receptor blockade (Esch et al. 2009; Sevá Pessôa et al. 2012). Indeed, simultaneous administration of β-Ile5-Ang II and candesartan lowered BP in spontaneously hypertensive rat (Jones et al. 2011).

5.2 ACE2-Ang-(1–7)-Mas Receptor Pathway

Angiotensin converting enzyme 2 (ACE 2) acts on angiotensin II to produce angiotensin (Ang)-(1–7) (Santos et al. 2003). Interaction of Ang-(1–7) and Mas receptor oppose AT_1 receptor functions. Further, Ang-(1–7) bind to AT_2 receptors and even AT_1 receptors at high doses. Several cardiovascular benefits have been attributed to Ang-(1–7), however its role in hypertension at present is unclear (Te Riet et al. 2015). Ang (1–7) has weak vasodilatory effects and has not uniformly exhibited anti-hypertensive effects in animal models (Sevá Pessôa et al. 2012; Durik et al. 2012).

Nevertheless, therapeutic options utilizing the vasoprotective effects of Ang-(1–7) have been explored. Cyclodextrin-encapsulated Ang-(1–7), non-peptide drug AVE0091 and peptide drug CGEN856S have shown BP-lowering effects in hypertensive animals (Sevá Pessôa et al. 2012; Ferreira et al. 2010).

Anti-hypertensive effects of ACE 2 have also been questioned. Overexpression of ACE 2 does lower blood pressure, however, its ability of degrade Ang-II could also account for anti-hypertensive effect (Gurley et al. 2006). Hypotension due to ACE 2 agonists Diminazine and XNT was recently shown to be independent of

ACE2-Ang-(1–7)-Mas pathway further weakening the evidence in support of its role in the pathogenesis of hypertension (Haber et al. 2014).

5.3 Alamandine

Alamandine, a recently discovered hormone of RAS, shares similar biological structure and activity to that of Ang-(1–7) including promotion of vasodilation and anti-hypertensive effects. ACE 2 hydrolyzation of Ang A and decarboxylation of Ang-(1–7) have both been shown to produce this endogenous peptide within the body (Villela et al. 2014). Lautner et al. demonstrated that alamandine interacts with its own specific MrgD receptor (Mas-related G-protein coupled receptor, member D) (Lautner et al. 2013). Oral administration of alamandine as a HP-B Cyclodextrin inclusion compound produced long term anti-hypertensive effect in spontaneously hypertensive rats (Lautner et al. 2013). Moreover, microinjections of almandine into the medullary brain demonstrated cardiovascular effects similar to that of Ang-(1–7), indicating a possible central role of BP control by alamandine (Villela et al. 2014; Mendoza-Torres et al. 2015). Further studies are required to delineate the role Alamandine plays in the RAAS, and as a anti-hypertensive agent.

5.4 Angiotensin III Inhibitors

Angiotensin III is a recognized AT_2 receptor agonist in the kidney and vasculature (Kemp et al. 2012). However, in the brain, it is believed to be the preferred AT_1 receptor agonist and therefore can cause hypertension (Wright et al. 2003). Aminopeptidase A inhibitors that act preferentially in the CNS to block Ang II conversion to Ang III are being developed. An orally administered prodrug (RB150), that converts to an aminopeptidase A inhibitor EC33 in the brain, exhibited antihypertensive effects in animal models. RB 150 is currently being evaluated in a phase Ib clinical study (Gao et al. 2014).

6 Aldosterone Mineralocorticoid Receptor Pathway

Aldosterone hormone activation of mineralocorticoid receptors (MR), a member of the steroid receptor family, is known to promote vascular cell oxidative stress, inflammation, proliferation, migration and extracellular matrix production (McCurley and Jaffe 2012; Lother and Hein 2016). Vaso-deleterious effects caused by MR activation include: vasoconstriction, atherosclerosis, and vascular remodeling and fibrosis (Lother and Hein 2016; Udelson et al. 2010). Nishiyama et al. demonstrated in animal models that mineralocorticoid-induced hypertension is associated with increased vascular oxidative stress and ROS production (McCurley and Jaffe 2012; Nishiyama and Abe 2004; Iglarz et al. 2004). Subsequently, MR antagonism showed a decrease in NADPH-oxidase activity, resulting in less ROS production, and thus lower BP (Keidar et al. 2003; Sanz-Rosa et al. 2005).

Activation of MR in the vascular bed is also associated with increased expression of proinflammatory factors including ICAM1, monocyte chemoattractant protein (MCP-1), cytokines, placental growth factor (PGF), COX-2 and transcription factor NF-κB (McCurley and Jaffe 2012; Rocha et al. 2002). Aortas from patients with atherosclerosis demonstrated a decrease in PGF and connective tissue growth factor when treated with spironolactone (a MR antagonist) (Jaffe et al. 2010; Newfell et al. 2011). Furthermore, the controlled Prevention and Treatment of Hypertension With Algorithm-Based Therapy (PATHWAY)-2- clinical trial showed a decrease in blood pressure by 8.7 mmHg with spironolactone treatment in patients with resistant hypertension (Lother and Hein 2016; MacDonald et al. 2015). Such findings support the role of MR-activation induced

inflammation as a contributing factor to hypertension. However, further trials exploring the use of MR antagonists as anti-hypertensive agents are required to confirm these results.

7 VEGF Inhibitors

Anti-angiogenesis therapy targeting vascular endothelial growth factor (VEGF) and its receptors as treatment for anti-tumor growth has long been associated with adverse side effects of hypertension and renal toxicity manifesting as proteinuria and renal function impairment (Lankhorst et al. 2016; van den Meiracker and Danser 2016). Physiologically, VEGF mediates vasodilation through increased nitric oxide (NO) production by upregulating the NOS gene expression and increased endothelial NOS phosphorylation (Hood et al. 1998; Shen et al. 1999). The subsequent decrease in NO availability following VEGF inhibition contributes to the pathogenesis of hypertension during anti-angiogenesis therapy (van den Meiracker and Danser 2016; Facemire et al. 2009). Recent investigations of the role of the Endothelin (ET) system, specifically Endothelin-1, suggest this system as a more significant contributor to the rise in BP compared to NO deprivation. A rise in ET-1 is noted with administration of sunitinib, a receptor tyrosine kinase (RTK) inhibitor that targets VEGF receptors (Kappers et al. 2010). Endothelin-1 (ET-1) interacts with G-protein-coupled membrane bound ET_A and ET_B receptors on vascular smooth muscle to mediate vasoconstriction. Furthermore, ET_A receptor antagonism prevented anti-angiogenic induced hypertension in mice (Li et al. 2012). Currently, there is no established guideline for reversing hypertension induced by VEGF-targeted therapies (Hayman et al. 2012).

8 Asymmetric Dimethylarginine

Asymmetric dimethyarginine (ADMA) is a naturally occurring amino acid synthesized when arginine residues in proteins undergo methylation by arginine methyltransferases (PRMTs) (Vallance and Leiper 2004; Vallance et al. 1992). An additional by-product of this interaction is N^G-monomethyl- L-arginine (L-NMMA), a methylarginine similar to ADMA in its biological activity. Following hydrolysis of methylated proteins ADMA and L-NMMA are released in the cytosol. ADMA is found in various tissues, circulates in plasma and is excreted in urine (Vallance and Leiper 2004). In addition to renal clearance, ADMA is extensively metabolized by dimethylarginine dimethyl aminohydrolases (DDAHs) resulting in conversion to citrulline (Achan et al. 2003).

Both ADMA and L-NMMA competitively inhibit all three isoforms NOS, thereby causing vasoconstriction, impaired endothelium-mediated vasodilatation, increased endothelial adhesiveness, and hypertension (Vallance et al. 1992; Achan et al. 2003; Hasegawa et al. 2007; Kielstein et al. 2004; Barba et al. 2000; Böger et al. 2000). Targeted deletion of DDAH gene and use of specific inhibitors of DDAH lead to accumulation of ADMA, a reduction in NO signaling and subsequent vascular dysfunction, increased systemic vascular resistance and blood pressure (Leiper et al. 2007). Transgenic mice overexpressing DDAH demonstrated reduced ADMA levels and increased cardiac NO levels. However, transgenic mice showed no changes in systemic BP compared to wild type controls under normal conditions (Hasegawa et al. 2007). Two-week treatment with angiotensin II increased ADMA levels, cardiac oxidative stress and vascular injury while DDAH overexpression attenuated these changes (Hasegawa et al. 2007). Conversely, Jacobi et al. reported no increase in ADMA levels following 4-week Ang II infusion (Jacobi et al. 2008). Overexpression of DDAH however attenuated ang-II medicated end organ damage (Jacobi et al. 2008).

Small clinical studies have noted an association between hypertension and increased ADMA levels (Surdacki et al. 1999; Perticone et al. 2005). Larger scale clinical studies have however not corroborated these findings (Meinitzer et al. 2007; Schnabel et al. 2005). Trials evaluating the effect of antihypertensive agents on ADMA levels have yielded conflicting results. Some

investigators reported significant reductions in ADMA levels following treatment with RAS, (Chen et al. 2002; Delles et al. 2002; Ito et al. 2002; Napoli et al. 2004; Aslam et al. 2006) while others have failed to confirm these findings (Fliser et al. 2005; Warnholtz et al. 2007). Differences in study design, treatment regimens, methods of determining ADMA levels may account for the discrepant findings of the aforementioned studies.

ADMA has been shown to have a negative correlation with endothelial-dependent vasodilation (EDV) and a positive correlation with carotid artery intima-media thickness (IMT) in hypertensive patients with administration of salbutamol and nitroglycerine (Serg et al. 2011). Cakar and colleagues evaluated arterial stiffness markers for endothelial dysfunction and found that ADMA levels significantly correlated with augmentation index (Aix) and CRP levels. However, there was no correlation between PWV and central aortic pressure (CAP) and ADMA (Cakar et al. 2015). Similarly, the PREVENCION study showed that ADMA and NMMA did not predict carotid-femoral PWV, blood pressure or hemodynamic abnormalities (Chirinos et al. 2008). Therefore, while it is very clear that ADMA plays a role in endothelial dysfunction and can cause significant changes in vascular flow, it still remains to be seen whether ADMA directly play a role in hypertension.

Therapeutic approaches specifically targeting ADMA pathways have been studied. Increased L-citrulline supplementation overcame ADMA inhibition, resulting in improved NO production in porcine hearts (Xuan et al. 2015). The effects of L-arginine on endothelial function, blood pressure, and ADMA levels in patients with hypertension (NCT02392767) and in patients with preeclampsia are currently being evaluated (NCT00275158).

9 Conclusion

The recently concluded SPRINT trial has suggested that achieving aggressive blood pressure targets reduces cardiovascular morbidity and mortality. This will require more aggressive and complex treatment regimens, in most cases with multi-drug protocols. In order to achieve better blood pressure control, it is imperative to understand the mechanisms that lead to increased blood pressure. Knowledge of the causative mechanisms will allow informed selection of agents and combinations that are additive and even synergistic. Such an approach will in turn allow the fashioning "personalized" treatment regimens that will maximally benefit each patient individually.

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