The Role of Chemokines in Hypertension

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Abstract

Hypertension is a major risk factor for cardiovascular disease, which is a serious health problem in the highly industrialized countries. In more than 95% of the cases, the etiology of hypertension remains unknown. A key role in the etiology of hypertension is played by endothelial dysfunction and the inflammatory reaction in the vascular wall, in which the low molecular weight proteins – so-called chemokines – are involved. The chemokines involved in the pathogenesis of hypertension include monocyte chemoattractant protein-1, MCP-1, CCL2, interferon-inducible protein (IP-10; CXCL10), interleukin-8 (IL-8; CXCL8), RANTES (CCL5), fractalkine (CX3CL1) and their receptors CCR2, CCR5, CXCR1, CXCR2, CXCR3, and CX3CR1. The mechanisms involving chemokines and their receptors in the pathogenesis of hypertension are complex and not fully understood. They include the impact of the migration of macrophages and monocytes to the vascular wall, endothelial dysfunction, effects on nitric oxide and endothelin-1 and smooth muscle cell proliferation. Chemokines are also involved in the pathogenesis of complications of hypertension, such as atherosclerosis, myocardial and renal fibrosis. In Poland, only about 26% of patients are effectively treated with antihypertensive drugs. The use of new therapeutic methods based on the inhibition of the inflammatory process in the vascular wall, including the impact on the function of chemokines and their receptors, could improve the effectiveness of the treatment of hypertension (Advan Clin Exp Med 2014, 23, 3, 319–325).

Key words: hypertension, chemokines, endothelium.
chemokine. Four major classes of chemokines have been described: CXC, CC, C and CX3C. The primary function of chemokines is inducing the migration of leukocytes to the damaged vascular wall and ligand-receptor binding to receptors present on leukocytes. Under the influence of chemokines, monocytes infiltrate tissue and differentiate into macrophages; the monocytes secrete chemokines and cytokines while exacerbating inflammation.

Chemokines play the role of chemoattractants, but also play a variety of roles in the body: They are involved in angiogenesis, hematopoiesis, embryogenesis, organogenesis, the maturation of dendritic cells, tumor growth, tumor metastasis, autoimmune and inflammatory processes as well as the promotion of cancer cell growth. These proteins are secreted constitutively and after induction. Induced chemokines are produced by tissues and leukocytes in response to bacterial toxins and inflammatory cytokines such as interleukine-1 (IL-1), tumor necrosis factor (TNF-α) and interferons. Changes in the expression of chemokines and their receptors have been observed in rheumatoid arthritis, multiple sclerosis, asthma and atherosclerosis. Chemokines also play an important role in the control of inflammation in the walls of blood vessels in hypertension. The inflammatory infiltrate and oxidative stress in the vascular wall cause an increase in blood pressure, and inhibition of these processes results in a decrease in blood pressure [2]. Chemokines participate in the migration of leukocytes in the course of hypertension not only into the blood vessel wall, but also to the kidneys [3] and the heart [4].

The chemokines taking part in the pathogenesis of hypertension include monocyte chemoattractant protein-1 (MCP-1, CCL2), interferon-inducible protein (IP-10, CXCL10) interleukin-8 (IL-8; CXCL8), Gro-α (growth-related oncogene), CXCL1/RANTES (CCL5)/CCR5 and fractalkine (CX3CL1)/CX3CR1.

The Role of MCP-1 in the Pathogenesis of Hypertension

Monocyte chemo-attractant protein-1 (MCP-1) is a C-C chemokine (CCL2). MCP-1 is produced constitutively and can be induced by oxidative stress, cytokines and growth factors. This protein is synthesized by the cells of blood vessels, cardiac muscle and the kidneys in response to hemodynamic stimuli (shear stress, blood flow) or hormone stimuli (angiotensin II, endothelin-1). N-nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a protein complex present in the cytoplasm of cells that can be activated by a number of inflammatory factors, such as TNF-α, interleukins, lymphotoxins, liposaccharides, oxidized low-density lipoprotein (LDL) and reactive oxygen species (ROS). NF-κB acts as a transcription factor that controls the expression of MCP-1 and IL-8 and the expression of adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells and vascular smooth muscle cells.

By activating the CCR2 receptor, MCP-1 activates monocyte and leukocyte migration to sites of inflammation. Elevated MCP-1 expression has been observed in atherosclerosis and angina pectoris, including unstable angina [5], both in animal models and in clinical trials. By activating CCR2, angiotensin II stimulates proliferation of the smooth muscle cells of the aorta, which is a significant process in the pathogenesis of hypertension, arteriosclerosis and vascular stent restenosis [6]. A lack of functional CCR5 and CCR2 receptors may be associated with the emergence of hypertension [7]. These receptors are located on T cells, macrophages, dendritic cells and microglia [8]. A study investigating the relationship between blood pressure level and CCR5 and CCR2 receptor gene polymorphism showed a statistically significant association between CCR5 Delta32 gene polymorphism and elevated blood pressure values, which indicates the importance of this gene in the regulation of blood pressure [9]. In another study, on a larger group of patients with hypertension, no evidence of this association was found [10].

Animal studies have shown that CCL2 chemokine activity in the brain can have a significant impact on neurogenic hypertension. Inhibition of CCL2 expression and its receptors CCR1 and CCR2 in the brainstem unexpectedly contributes to increased blood pressure in spontaneously hypertensive rats. In animals injected with CCL5 in the vicinity of the nucleus tractus solitarius of the brain, a decrease in blood pressure was observed. Moreover, this effect was much less evident in control rats not affected by hypertension [11].

Numerous studies using animal models of hypertension showed the benefits of MCP-1/CCR2 blockade. In rats with hypertension induced by blocking the synthesis of nitric oxide (NO), MCP-1/CCR2 blockade had an anti-inflammatory effect [12]. The use of RS 102895 (a CCR2 receptor blocker) caused a reduction in blood pressure, possibly as a result of an anti-inflammatory effect by inhibiting NFκB activation in the kidneys, expression of TNF-α and ICAM-1. In spontaneously hypertensive rats, NFκB blockade prevents the
emergence of high blood pressure and lowers the heart rate, which was not observed in normotensive rats [13]. CCR2 receptor blockade may therefore be effective in the prevention of hypertension.

The use of angiotensin receptor blockers reduces the level of MCP-1. Valsartan inhibits the expression of MCP-1 and TNF-α, interleukin-6 (IL-6), interleukin-1β (IL-1β) and the infiltration of leukocytes and macrophages into the vascular wall [14]. In spontaneously hypertensive rats, telmisartan and losartan (AT1R receptor antagonists) inhibit the expression of MCP-1 and its receptor in the aorta and in monocytes, and lower MCP-1 levels in the serum [15]. Olmesartan lowers the activity of NADPH oxidase (one of the most important sources of oxygen-derived free radicals), the expression of MPC-1 and TGF-β-1, inhibits fibrosis, left ventricular hypertrophy and diastolic dysfunction in rats with hypertension induced by sodium chloride [16]. Of particular interest is the fact that patients with hypertension and hypercholesterolemia, the administration of statin and RAS blockers was more effective in reducing levels of MCP-1 than either of these methods alone [17], indicating that the interaction of statin and RAS blockers exerts a super-additive effect in patients with hypertension. As demonstrated in experimental trials, PPAR-γ receptor agonists are also effective in reducing the level of MCP-1 [18]. Telmisartan is an antihypertensive drug combining the properties of RAAS blockade and effects on PPAR-γ; it has both antihypertensive and anti-inflammatory properties by combining PPAR-γ activation and the impact of the so-called advanced glycation end products in patients with diabetic nephropathy [19]. Telmisartan is more effective than amlodipine in reducing MCP-1 levels in patients with essential hypertension [20]. Despite increases in the expression of CD11b, CD54 and CCR5 receptors, telmisartan blocks the adhesion of monocytes to endothelial cells, preventing the process of atherogenesis [21].

Angiotensin II present in the renal tissue of hypertensive rats induces inflammation, oxidative stress and deterioration of renal function, increased concentrations of MCP-1, TNF-α, TGF-β and NFκB. Angiotensin receptor blocker (candesartan) reduces angiotensin II levels in the kidney tissue, thus showing anti-inflammatory and nephroprotective activity [22].

Studies using animal models have shown that MCP-1 plays an important role in the process of myocardial fibrosis. In mice lacking the CCR2 gene, angiotensin II administration caused cardiac hypertrophy and hypertension, but due to its function inhibiting fibroblast precursor infiltration, it did not induce cardiac fibrosis. In these mice, left ventricular dilatation and systolic dysfunction with preserved diastolic function of the heart were observed. The CCR2 receptor is involved in the process of angiotensin-induced cardiac fibrosis, but does not protect against complications in the form of dilatation and systolic dysfunction [23]. Greater expression of the genes for the CCR2 receptor, CXCR4 and CCR7 has been noted in patients with hypertensive heart disease as compared to normotensive controls [24]. MCP-1 is involved not only in the migration of leukocytes to the vascular wall, but also participates in the pathogenesis of hypertensive heart disease.

MCP-1 plays a role in the pathogenesis of kidney diseases that lead to the development of hypertension, such as diabetic nephropathy [25], Goodpasture’s syndrome [26] or renal artery stenosis. Renal artery stenosis leads to secondary activation of the RAAS, increased expression of MPC-1, inflammation, oxidative stress, impaired renal function and hypertension. Administration of bindarit, which decreases MCP-1 expression, decreased the level of oxidative stress in the tubulo-interstitial compartment, but it did not affect blood pressure [27]. RS 102895, a CCR2 inhibitor, reduces monocyte infiltration in the kidneys of rats with sodium-dependent hypertension and microalbuminuria [28], indicating possible inhibition of the development of hypertensive nephropathy by blockade of CCR2. In studies using animal models of hypertension, high expression of the CCR2 gene and its agonists CCL2, CCL7, CCL8 and CCL12 has been found. INCB3344, a CCR2 antagonist, inhibits the expression of CCR2, infiltration of macrophages and decreased blood pressure in hypertensive mice [29].

In studies using spontaneously hypertensive rats it has been found that a diet supplemented with 1% azuki beans (Vigna angularis), containing significant amounts of polyphenols, lowers blood pressure, oxidative stress, MCP-1 and CCR2 expression, which may indicate that recommending a diet with high antioxidant content is appropriate in hypertension [30].

In summary, despite numerous studies in animal models and in vitro studies which indicate the role of CCL2/CCR2 in the development of hypertension and the effectiveness of its blockade in preventing hypertension and its cardiac and renal complications, there is still no convincing evidence in the form of clinical trials and epidemiological studies. It should be noted, however, that many of the drugs currently in use in hypertensive therapy - including ACE inhibitors, angiotensin receptors or calcium channel blockers - have the ability to inhibit the expression of MCP-1 and to block CCR2 receptors.
IL-8, IP-10 and Fractalkine in Hypertension

The chemokine CXCL8 (IL-8) belongs to the CXC chemokine family, and has an affinity to CXCR1 (type 1 receptor for IL-8) and CXCR2 receptors (type 2 receptor for IL-8). These receptors, present on endothelial cells, are activated by Rho and Rac signaling pathways. CXCL8 participates in the pathogenesis of hypertension, as demonstrated in animal models. Higher values of this chemokine have been found in spontaneously hypertensive rats (SHRs) as compared with control rats. In SHRs, angiotensin II induced IL-8 expression in smooth muscle cells, while losartan (an angiotensin receptor inhibitor) inhibited its action [31]. This chemokine also stimulates proliferation and inhibits endothelial cell apoptosis, which plays a key role in the regulation of blood pressure [32].

IL-8 plays an important role in the migration of leukocytes into the sub-endothelial vascular wall in the early stages of atherosclerosis, and increased level of the chemokine is associated with a higher risk of coronary heart disease [33]. When given intravenously to rats with hypertension, reparixin, an IL-8 receptor inhibitor, caused a reduction in blood pressure, decreased expression of CXCL-8, CCL2, 12-lipoxygenase (LO), endothelin-1 (ET)-1 and angiotensin AT1 receptor. In these rats, a higher concentration of nitric oxide was also observed [34].

IL-8 is able to induce gene expression of 12-15-lipoxygenase (12-LO) in porcine aortic smooth muscle cells. IL-8, 12-LO and the arachidonic acid pathway play an important role in the pathogenesis of hypertension [35]. Angiotensin II, one of the strongest vasoconstrictors, stimulates the activation and expression of 12-LO in porcine and human aortic smooth muscle cells. IL-8 is able to induce 12-LO by acting on the AT-1 receptor in smooth muscle cells of spontaneously hypertensive rats.

Interferon-inducible protein (IP-10) is a chemokine from the CXCL family (CXCL10). In a study by Antonelli et al., patients with essential hypertension had higher values of this chemokine and of CCL2 (described above) than the control group. The highest values of IP-10 were observed in patients with complications of hypertension such as microalbuminuria [36]. IP-10 affects vascular smooth muscle cell migration and the permeability of the endothelial cell layer [37]. The level of IP-10, as well as the I-309 (CCL1) chemokine, is lowered by angiotensin-converting-enzyme inhibitors (perindopril and imidapril) in TH-1 cells and human monocytes [38].

Fractalkine (CXCL1), a chemokine occurring both in soluble form and bound to the cell membranes, participates in the pathogenesis of atherosclerosis and hypertension, as demonstrated in animal models [39]. The form bound to the cell membrane participates in the uptake and adhesion of leukocytes under physiological flow, while the soluble form is involved in the uptake of monocytes, NK cells and T cells in peripheral tissues [40]. Wong et al. observed fractalkine expression in vessels of patients with atherosclerosis, diabetes and post-transplantation vasculopathy [41]. Ex vivo studies showed that fractalkine has the ability to inhibit apoptosis in human monocytes. In vascular endothelial cells and renal glomeruli CX3CR1 fractalkine and its receptors exacerbate inflammation and interstitial fibrosis [42]. CXCL1/CX3CR1 also participate in the process of renal fibrosis in the course of hypertension leading to increased expression if TGF-β [1] and collagen type 1 [43].

Chemokines and Endothelial Dysfunction

Endothelial dysfunction plays a key role in the pathogenesis of hypertension. A properly functioning endothelium participates in the relaxation of blood vessels, exerts an anti-inflammatory and anticoagulant effect, inhibits smooth muscle cell proliferation and the migration of leukocytes to the vascular wall. Endothelial dysfunction allows leukocyte adhesion and accumulation in the intima of the vascular wall. Chemokines are not only involved in migration and adhesion of mononuclear leukocytes, but also negatively impact the activity of the vascular protective factor (NO), intensifying endothelial dysfunction and leading to vasoconstriction and blood pressure elevation.

One of the most important indicators of endothelial dysfunction is impairment of functions that are dependent on NO. Since NO has the ability to inhibit the expression of MCP-1, in endothelial dysfunction MCP-1 and leukocyte migration are activated, increasing inflammation in the vascular wall. Elevated concentrations of MCP-1 have been described in patients with essential hypertension and endothelial dysfunction [44]. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of NO synthase which, through a reduction in its bioavailability, can lead to endothelial dysfunction. ADMA is capable of inducing oxidative stress and the production of MCP-1 in human vascular endothelial cells [45].

Angiotensin II not only stimulates the production of MCP-1 by activating NF-kB, but also induces oxidative stress in the vascular wall.
Angiotensin II exerts its effect via receptors present on the cell surface, mainly AT1 and AT2 (angiotensin II tissue receptor subtypes 1 and 2). The activation of the AT1 receptor leads to the excitation of a number of signaling pathways (including phospholipases, adenylate cyclase and kinases), which in turn increases ROS production, increases contractile and hypertensive activity, and also stimulates the proliferation of smooth muscle cells of the vascular wall. Increased ROS production results in decreased NO activity and thereby intensifies leukocyte migration and inflammation in the vascular wall. Angiotensin II also stimulates the expression of CX3CR1, a fractalkine receptor in the arteries [46]. In vitro studies have shown that fractalkine is able to induce ROS, including superoxide ions, which results in reduced availability of NO and endothelial dysfunction [47].

A state of dynamic equilibrium between vaso-dilative, antithrombotic and anti-inflammatory factors (mainly NO) and vasoconstrictive, pro-thrombotic and pro-inflammatory factors (endothelin-1, ET-1) play a key role in the regulation of blood pressure. The chemokine CXCL-8 stimulates the production of ET-1 and plasminogen activation inhibitor 1 (PAI-1) in endothelial cells, disrupting endothelial homeostasis and intensifying pro-coagulant and vasoconstrictive activity, which leads to endothelial dysfunction [48]. Oxidative stress induces the expression of a new transcription factor (ZNF580) and by the NF-κB signaling pathway stimulates the release of CXCL-8 in the endothelium cells [49]. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase blockade, one of the main sources of ROS in endothelial cells, inhibits the expression of CXCL-8 through a calcium channel blocker, azelnidipine, and has an anti-inflammatory and anti-atherogenic effect [50].

Endothelial dysfunction and leukocyte infiltration in the subendothelial space are key processes in the pathogenesis not only of hypertension but also its complications such as atherosclerosis, stroke and coronary heart disease. The following chemokine-receptor pairs play a vital role in the activation of leukocyte infiltration of the vascular wall: MCP-1/CCR2, RANTES/CCR5, fractalkine/CX3CR1, II-8/CXCR2 and GRO-α/CXCL1 [51]. In addition, the pairs MCP-1/CCR2 and fractalkine/CX3CR1 are involved in the proliferation of smooth muscle cells. Gro-α (CXCL-1)/CXCR2 inhibits neointima formation, which promotes the regeneration of endothelial cells [52]. Endothelial dysfunction can lead to vascular remodeling, vascular stiffness and the development of vascular complications of hypertension, such as hypertensive heart disease, stroke and kidney failure. Many drugs that are currently in use improve endothelial function via mechanisms associated with chemokines and their receptors. These drugs include angiotensin converting enzyme inhibitors (described above), angiotensin receptor blockers, calcium channel blockers and newer generation beta-blockers.

Conclusions

Chemokines and their receptors play an important role in the development of endothelial dysfunction and hypertension. The mechanisms involving chemokines and their receptors in the pathogenesis of hypertension are complex and not fully understood. They include influence on the activation and migration of monocytes and macrophages into the vascular wall, endothelial dysfunction, vascular smooth muscle cell proliferation and increased severity of hypertension complications such as atherosclerosis, hypertensive heart disease and hypertensive nephrosclerosis. Many drugs currently in use affect the function of chemokines and their receptors through their impact on the RAAS system, oxidation-reduction reactions and PPAR-γ receptors. The effectiveness of treatment of hypertension in Poland has improved in recent years, but only 26% of patients are effectively treated. Understanding the full role of chemokines in the pathogenesis of hypertension may have important practical implications. The application of new therapeutic methods based on the inhibition of inflammation in the vascular walls, including its impact on the function of chemokines and their receptors, could improve the efficacy of the treatment of hypertension and its complications.

References


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