EDITORIAL

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The Role of Chemokines in Hypertension

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

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 (**Adv Clin Exp Med 2014, 23, 3, 319–325**).

Key words: hypertension, chemokines, endothelium.

Hypertension is one of the most important risk factors for cardiovascular diseases. In Poland, cardiovascular diseases pose a major medical, economic and social problem. The prevalence of hypertension in Poland reaches 32% of the adult population, but only one in three Poles suffering from hypertension is aware of the disease [1]. In more than 95% of the cases, the etiology of essential hypertension remains unknown. A significant role in the pathogenesis of hypertension is played by genetic factors regulating the transport of ions and water, renal hemodynamics and the function of numerous hormones such as aldosterone, catecholamines, renin, vasopressin and endothelin-1 (ET-1). The level of blood pressure depends on the interplay of numerous systems and factors such as the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, natriuretic peptides and the vascular endothelium. Blood pressure level is also affected by factors such as sodium intake, low physical activity, stress and obesity. In recent years, attention has been paid to the participation of inflammatory factors in the etiology of hypertension leading to endothelial dysfunction, which in turn plays a key role in the pathogenesis of hypertension. Low molecular weight proteins of the cytokine family which have the ability to stimulate and control leukocyte migration – so-called chemokines – participate in the inflammatory reaction involving the vascular wall. These proteins have the ability to bind to receptors associated with 7-transdomain G proteins; however, most chemokines bind to more than one receptor, and the receptors are capable of binding more than one

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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 intrleukine-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 in patients with hypertension and hypercholestrolemia, the administration of statin and RAAS 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-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 (peridopril 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-κB, 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 vasodilative, 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, Il-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

[1] **Zdrojewski T, Bandosz P, Gaciong Z, Wyrzykowski B:** Rozpowszechnienie czynników ryzyka chorób układu sercowo-naczyniowego w Polsce w 2011 r. Zakres wieku 18–79 lat. NATPOL 2011. XV Międzynarodowy Kongres PTK. Wrocław 6–8.10.2011

[2] **Rodríguez-Iturbe B, Vaziri ND, Herrera-Acosta J, Johnson RJ:** Oxidative stress, renal infiltration of immune cells andsalt-sensitive hypertension: all for one and one for all. Am J Physiol 2004, 286, 606–616.

[3] **Johnson RJ, Alpers CE, Yoshimura A, Lombardi D, Pritzl P, Floege J, Schwartz SM:** Renal injury from angiotensin II-mediated hypertension. Hypertension 1992, 19, 464–474.

[4] **Haller H, Behrend M, Park JK, Schaberg T, Luft FC, Distler A:** Monocyte infiltration and c-fms expression in hearts of spontaneously hypertensive rats. Hypertension 1995, 25, 132–138.

[5] **Aukrust P, Berge, RK, Ueland T, Aaser E, Damås JK, Wikeby L, Brunsvig A, Müller F, Forfang K, Frøland SS, Gullestad L:** Interaction between chemokines and oxidative stress possible pathogenic role in acute coronary syndromes. J Am Coll Cardiol 2001, 37, 485–491.
[6] **Yao HL, Gao FH, Li ZZ, Wu HX, Xu MD, Zhang Z, Dai QY:** Monocyte chemoattractant protein-1 mediates angiotensin II-induced vascular smooth muscle cell proliferation via SAPK/JNK and ERK1/2. Mol Cell Biochem 2012, 366, 355–362.
[7] **Mettimano M, Specchia ML, Ianni A, Arzani D, Ricciardi G, Savi L, Romano-Spica V:** CCR5 and CCR2 gene polymorphisms in hypertensive patients. Br J Biomed Sci 2003, 60, 19–21.
[8] **Arenzana-Seisdedos F, Parmentier M:** Genetics of resistance to HIV infection: Role of co-receptors and co-receptor ligands. Semin Immunol 2006, 18, 387–403.
[9] **Mettimano M, Specchia ML, La Torre G, Bruno A, Ricciardi G, Savi L, Romano-Spica V:** Blood pressure regulation by CCR genes. Clin Exp Hypertens 2006, 28, 611–618.
[10] **Zhang M, Ardlie K, Wacholder S, Welch R, Chanock S, O'Brien TR:** Genetic variations in CC chemokine receptors and hypertension. Am J Hypertens 2006, 19, 67–72.
[11] **Gouraud SS, Waki H, Bhuiyan ME, Takagishi M, Cui H, Kohsaka A, Paton JF, Maeda M:** Down-regulation of chemokine Ccl5 gene expression in the NTS of SHR may be pro-hypertensive. J Hypertens 2011, 29, 732–740.
[12] **Koyanagi M, Egashira K, Kitamoto S, Ni W, Shimokawa H, Takeya M, Yoshimura T, Takeshita A:** Role of monocyte chemoattractant protein-1 in cardiovascular remodeling induced by chronic blockade of nitric oxide synthesis. Circulation 2000, 102, 2243–2248.
[13] **Rodriguez-Iturbe B, Ferrebuz A, Vanegas V, Quiroz Y, Mezzano S, Vaziri ND:** Early and sustained inhibition of nuclear factor-kappa B prevents hypertension in spontaneously hypertensive rats. J Pharmacol Exp Ther 2005, 315, 51–57.
[14] **Wu L, Iwai M, Nakagami H:** Roles of angiotensin II type 2 receptor stimulation associated with selective angiotensin II type 1 receptor blockade with valsartan in the improvement of inflammationinduced vascular injury. Circulation 2001, 104, 2716–2721.
[15] **Dai Q, Xu M, Yao M, Sun B:** Angiotensin AT1 receptor antagonists exert anti-inflammatory effects in spontaneously hypertensive rats. Br J Pharmacol 2007, 152, 1042–1048.
[16] **Nishio M, Sakata Y, Mano T, Yoshida J, Ohtani T, Takeda Y, Miwa T, Masuyama T, Yamamoto K, Hori M:** Therapeutic effects of angiotensin II type 1 receptor blocker at an advanced stage of hypertensive diastolic heart failure. J Hypertens 2007, 25, 455–461.
[17] **Koh KK, Quon MJ, Han SH, Chung WJ, Ahn JY, Seo YH, Kang MH, Ahn TH, Choi IS, Shin EK:** Additive beneficial effects of losartan combined with simvastatin in the treatment of hypercholesterolemic, hypertensive patients. Circulation 2004, 14, 110, 3687–3692.
[18] **Pasceri V, Chang J,Willerson JT, Yeh ET:** Modulation of C-reactive protein-mediated monocytechemoattractant protein-1 induction in humanendothelial cells by anti-atherosclerosis drugs. Circulation 2001, 103, 2531–2534.
[19] **Matsui T, Yamagishi S, Ueda S, Nakamura K, Imaizumi T, Takeuchi M, Inoue H:** Telmisartan, an angiotensin II type 1 receptor blocker, inhibits advanced glycation end-product (AGE)-induced monocyte chemoattractant protein-1 expression in mesangial cells through downregulation of receptor for AGEs via peroxisome proliferator-activated receptor-gamma activation. J Int Med Res 2007, 35, 482–489.
[20] **Marketou ME, Kontaraki JE, Tsakountakis NA, Zacharis EA, Kochiadakis GE, Arfanakis DA, Parthenakis F, Chlouverakis G, Vardas PE:** Differential effect of telmisartan and amlodipine on monocyte chemoattractant protein-1 and peroxisome proliferator-activated receptor-gamma gene expression in peripheral monocytes in patients with essential hypertension. Am J Cardiol 2011, 107, 59–63.
[21] **Syrbe U, Moebes A, Scholze J, Swidsinski A, Dörffel Y:** Effects of the angiotensin II type 1 receptor antagonist telmisartan on monocyte adhesion and activation in patients with essential hypertension. Hypertens Res 2007, 30, 521–528.
[22] **Lin L, Phillips WE, Manning RD:** Intrarenal Angiotensin ii is associated with inflammation, renal damage and dysfunction in dahl salt-sensitive hypertension. J Am Soc Hypertens 2009, 3, 306–314.
[23] **Ji Xu J, Lin SC, Chen J, Miao Y, Taffet GE, Entman ML, Wang Y:** CCR2 mediates the uptake of bone marrow-derived fibroblast precursors in angiotensin II-inducd cardiac fibrosis. Am J Physiol Heart Circ Physiol 2011, 301, 538–547.
[24] **Keeley EC, Mehrad B, Janardhanan R, Salerno M, Hunter JR, Burdick MM, Field JJ, Strieter RM, Kramer CM:** Elevated circulating fibrocyte levels in patients with hypertensive heart disease. J Hypertens 2012, 30, 1856–1861.
[25] **Giunti S, Barutta F, Perin PC, Gruden G:** Targeting the MCP-1/CCR2 System in diabetic kidney disease. Curr Vasc Pharmacol 2010, 8, 849–860.
[26] **Urushihara M, Ohashi N, Miyata K, Satou R, Acres OW, Kobori H:** Addition of angiotensin II type 1 receptor blocker to CCR2 antagonist markedly attenuates crescentic glomerulonephritis. Hypertension 2011, 57, 586–593.
[27] **Zhu XY, Chade AR, Krier JD, Daghini E, Lavi R, Guglielmotti A, Lerman A, Lerman LO:** The chemokine monocyte chemoattractant protein-1 contributes to renal dysfunction in swine renovascular hypertension. J Hypertens 2009, 27, 2063–2073.
[28] **Elmarakby AA, Quigley JE, Olearczyk JJ, Sridhar A, Cook AK, Inscho EW, Pollock DM, Imig JD:** Chemokine receptor 2b inhibition provides renal protection in angiotensin II – salt hypertension. Hypertension 2007, 50, 1069–1076.
[29] **Chan CT, Moore JP, Budzyn K, Guida E, Diep H, Vinh A, Jones ES, Widdop RE, Armitage JA, Sakkal S, Ricardo SD, Sobey CG, Drummond GR:** Reversal of vascular macrophage accumulation and hypertension by a CCR2 antagonist in deoxycorticosterone/salt-treated mice. Hypertension 2012, 60, 1207–1212.

[30] **Mukai Y, Sato S:** Polyphenol-containing azuki bean (*Vigna angularis*) seed coats attenuate vascular oxidative stress and inflammation in spontaneously hypertensive rats. J Nutr Biochem 2011, 22, 16–21.
[31] **Kim HY, Kang YJ, Song IH, Choi HC, Kim HS:** Upregulation of interleukin-8/CXCL8 in vascular smooth muscle cells from spontaneously hypertensive rats. Hypertens Res 2008, 31, 515–523.
[32] **Li A, Dubey S, Varney ML, Dave BJ, Singh RK:** IL-8 directly enhanced endothelial cell survival, proliferation, and matrix metalloproteinases production and regulated angiogenesis. J Immunol 2003, 170, 3369–3376.
[33] **Boekholdt S, Peters R, Hack CE, Day NE, Luben R, Bingham SA, Wareham NJ, Reitsma PH, Khaw KT:** IL-8 plasma concentrations and the risk of future coronary arterydisease in apparently healthy men and women. Arterioscler Thromb 2004, Vasc Biol 24, 1503–1508.
[34] **Kim HY, Choi JH, Kang YJ, Park SY, Choi HC, Kim HS:** Reparixin, an inhibitor of CXCR1 and CXCR2 receptor activation, attenuates blood pressure and hypertension-related mediators expression in spontaneously hypertensive rats. Biol Pharm Bull 2011, 34, 120–127.
[35] **Preston IR, Hill NS, Warburton RR, Fanburg BL:** Role of 12-lipoxygenase in hypoxia-induced rat pulmonary artery smooth muscle cell proliferation. Am J Lung Cell Mol Physiol 2006, 290, 367–374.
[36] **Antonelli A, Fallahi P, Ferrari SM, Ghiadoni L, Virdis A, Mancusi C, Centanni M, Taddei S, Ferrannini E:** High serum levels of CXC (CXCL10) and CC (CCL2) chemokines in untreated essential hypertension. Int J Immunopathol Pharmacol 2012, 25, 387–395.
[37] **Talavera D, Castillo AM, Dominguez MC, Gutierrez AE, Meza I:** IL8 release, tight junction and cytoskeleton dynamic reorganization conducive to permeability increase are induced by dengue virus infection of microvascular endothelial monolayers. J Gen Virol 2004, 85, 1801–1813.
[38] **Tsai MK, Jan RL, Lin CH, Kuo CH, Yang SN, Chen HN, Huang MY, Hung CH:** Suppressive effects of imidapril on Th1- and Th2-related chemokines in monocytes. J Investig Med 2011, 59, 1141–1146.
[39] **White GE, Greaves DR:** Fractalkine: a survivor's guide: chemokines as antiapoptotic mediators. Arterioscler Thromb Vasc Biol 2012, 32, 589–594.
[40] **Fong AM, Robinson LA, Steeber DA, Tedder TF, Yoshie O, Imai T, Patel DD:** Fractalkine and CX3CR1 mediate a novel mechanism of leukocyte capture, firm adhesion, and activation under physiologic flow. J Exp Med 1998, 188, 1413–1419.
[41] **Wong BW, Wong D, McManus BM:** Characterization of Fractalkine (CX3CL1) and CX3CR1 in human coronary arteries with native atherosclerosis, diabetes mellitus, and transplant vascular disease. Cardiovasc Pathol 2002, 11, 332–338.
[42] **Koziolek MJ, Müller GA, Zapf A, Patschan D, Schmid H, Cohen CD, Koschnick S, Vasko R, Bramlage C, Strutz F:** Role of CX3C-chemokine CX3C-L/fractalkine expression in a model of slowly progressive renal failure. Nephrol Dial Transplant 2010, 25, 684–698.
[43] **Shimizu K, Furuichi K, Sakai N, Kitagawa K, Matsushima K, Mukaida N, Kaneko S, Wada T:** Fractalkine and its receptor, CX3CR1, promote hypertensive interstitial fibrosis in the kidney. Hypertens Res 2011, 34, 747–752.
[44] **De la Sierra A, Larrousse M:** Endothelial dysfunction is associated with increased levels of biomarkers in essential hypertension. J Hum Hypertens 2010, 24, 373–379.
[45] **Böger RH, Bode-Böger SM, Tsao PS, Lin PS, Chan JR, Cooke JP:** An endogenous inhibitor of nitric oxide synthase regulates endothelial adhesiveness for monocytes. J Am Coll Cardiol 2000, 36, 2287–2295.
[46] **Rius C, Piqueras L, González-Navarro H, Albertos F, Company C, López-Ginés C, Ludwig A, Blanes JI, Morcillo EJ, Sanz MJ:** Arterial and venous endothelia display differential functional fractalkine (CX3CL1) expression by angiotensin-II. Arterioscler Thromb Vasc Biol 2013, 33, 96–104.
[47] **Schäfer A, Schulz C, Fraccarollo D, Tas P, Leutke M, Eigenthaler M, Seidl S, Heider P, Ertl G, Massberg S, Bauersachs J:** The CX3C chemokine fractalkine induces vascular dysfunction by generation of superoxide anions. Arterioscler Thromb Vasc Biol 2007, 27, 55–62.
[48] **Cheng M, Li Y, Wu J, Nie Y, Li L, Liu X, Charoude HN, Chen H:** IL-8 induces imbalances between nitric oxide and endothelin-1, and also between plasminogen activator inhibitor-1 and tissue-type plasminogen activator in cultured endothelial cells. Cytokine 2008, 41, 9–15.
[49] **DangLi R, HeKong W, JiQin L, MingHua Z, WenCheng Z:** ROS-induced ZNF580 expression: a key role for H2O2/NF-κB signaling pathway in vascular endothelial inflammation. Mol Cell Biochem 2012, 359, 183–191.
[50] **Yamagishi S, Inagaki Y, Nakamura K, Imaizumi T:** Azelnidipine, a newly developed long-acting calcium antagonist, inhibits tumor necrosis factor-alpha-induced interleukin-8 expression in endothelial cells through its antioxidative properties. J Cardiovasc Pharmacol 2004, 43, 724–730.
[51] **Boisvert WA:** The participation of chemokines in atherosclerosis. Discov Med 2004, 4, 288–292.
[52] **Schober A:** Chemokines in Vascular Dysfunction and Remodeling, Arterioscler Thromb Vasc Biol 2008, 28, 1950–1959.

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