JSTMU Journal of Shifa Tameer-e-Millat University

https://j.stmu.edu.pk

Open Access

REVIEW ARTICLE

The cardiovascular system's Renin-Angiotensin-Aldosterone System (RAAS)

Lamiaa Saoud Abbod[1*], Fatima Amer Abd Algabar[2]

[1] Technical Demonstrator, Department of Nursing Technologies, Baquba Technical Institute, Middle Technical University, Diyala, Iraq

[2] Technical Demonstrator, Department of Nursing Technologies, Baquba Technical Institute, Middle Technical University, Diyala, Iraq

Author's Contribution

[1-2] Conceptualization and Writing

Article Info.

Conflict of interest: Nil

Funding Sources: Nil

Correspondence

Lamiaa Saoud Abbod

lamiaasaoud67@gmail.com

Cite this article as *Abbod LS, Algabar FA. Ahmad T, Abid R. Review: The cardiovascular system's Renin-Angiotensin-Aldosterone System (RAAS). JSTMU. 2023; 6(1):45-50.*

A B S T R A C T

The renin-angiotensin-aldosterone system (RAAS) has a noteworthy part in triggering, and inflammation is maintained by its physiological agents. A crucial mechanism for the initiation and headway of CVD, including Hypertension and atherosclerosis, is inflammation. In addition to its primary function in controlling blood pressure and its contribution to Hypertension, RAAS has pro-inflammatory and profibrotic cellular and molecular effects. Cardiovascular and renal disorders can be treated more effectively by hindering RAAS. Proof recommends that RAAS inhibition enhances vascular remodelling and gets better CVD sequels. Lower levels of oxidative stress and endothelial dysfunction, vascular inflammation, and favourable effects on endothelial progenitor cell regeneration are likely the causes of RAAS inhibition's sound vascular effects.

Keywords: *Renin-Angiotensin-Aldosterone System (RAAS), Hypertension, Atherosclerosis, Vascular Remodeling, CVD*

INTRODUCTION

Among the most crucial hormonal systems, the renin-angiotensin-aldosterone system Governors blood pressure, melted amount, and the balance of sodium and potassium to control the activities of the heart, kidneys, and adrenal glands.[1] More than a century ago, the classical RAAS system was found. 1934 Goldblatt et al. confirmed a Renin association between kidney blood pressure and activity.[2] At that juncture, numerous trial inquiries must be conducted to pinpoint the RAAS's constituent parts and their function in controlling blood pressure. A variety of cardiovascular disorders cardiovascular diseases (myocardial infarction, stroke, and congestive heart failure), renal malady, and CVD (Hypertension, atherosclerosis, and left ventricular hypertrophy) are all triggered by aberrant RAAS activity.[1]

Among the most crucial hormonal systems, the renin-angiotensin-aldosterone system Governors blood pressure, melted amount, and the balance of sodium and potassium to control the activities of the heart, kidneys, and adrenal glands. More than a century ago, the classical RAAS system was found. 1934 Goldblatt et al. confirmed a Renin association between kidney blood pressure and activity.[2] Numerous trial inquiries were needed to pinpoint the RAAS's constituent parts and their function in controlling blood pressure. A variety of cardiovascular disorders Cardiovascular diseases (myocardial infarction, stroke, and congestive heart failure), renal malady, and CVD (Hypertension, atherosclerosis, and left ventricular hypertrophy) are all triggered by aberrant RAAS activity.

RAAS:

Prorenin, a torpid preprohormone that is later renovated into renin, an active proteolytic enzyme, before being released into circulation, takes place in the renal glomerulus' afferent arterioles.[3, 4] Proteolytic and no proteolytic processes hew prorenin to the present renin in the bloodstream. Angiotensin I is produced by active renin's reaction with its substrate, angiotensinogen (Ang I). Angiotensin-converting enzyme (ACE) breaks down Ang I to fabricate physiologically active Angiotensin II (Ang II). The primary RAAS effector, Ang II, conveys its actions through the type 1 Ang II receptor (AT1R). Little research points to additional prorenin and renin receptors in the heart, kidney, liver, and placenta.[5] Other investigations indicate that visceral and subcutaneous adipose tissues have renin receptors, indicating a local generation of Ang II. Prorenin and renin receptor activation activate a signaling pathway connected to a mitogen-activated kinase (MAPK) and extracellular signal-regulated kinase (ERK1/2).[6] Since renin regulates the rate-limiting stage of RAAS, the notion of impeding renin to reduce RAAS was proposed in the middle of the 1950s. Nevertheless, the stayed of renin inhibitors was a delayed and challenging procedure.[7]

Cardiovascular Disease and Inflammation

Numerous cardiovascular diseases, including Hypertension, atherosclerosis, restenosis following balloon angioplasty, nephropathy, and cardiomyopathy, are primarily attributed to inflammation in their onset, progression, and development.[8] A common illustration of how irritation drives the onset of cardiovascular disease is atherosclerosis, caused by stirring cytokines activating endothelial cells. Cardiovascular menace elements like Hypertension, diabetes, or obesity have been linked to endothelium dysfunction brought on by inflammation-induced injury.[9]

Markers of Inflammation

In practically all cell types, polyp necrosis element alpha (TNF) is a crucial pro-inflammatory cytokine that controls the articulation of several genes involved in soreness, oxidative stress, and anti-apoptotic signing lanes.[10] Therapeutic TNF signaling inhibition has been offered in dealing with several inflammatory disorders, especially rheumatoid arthritis and bowel disease. Aberrant TNF signaling promotes the progress of unreasonable settings, such as cardiovascular disease. By generating superoxide radicals, TNF reduces the endothelium-dependent nitric oxide (NO) mediated vasorelaxation in coronary or carotid arteries.[11] cardiovascular diseases are more likely to develop in patients with elevated ranks of circulating TNF. TNF promotes the invention of cell adhesion molecules (CAM), monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6) in endothelial cells [21]. Mice lacking TNF are less likely to experience intimal hyperplasia following carotid artery damage, whereas mice with higher levels of TNF expression experience worsening pulmonary Hypertension.[12] Vascular remodeling is significantly influenced by TNF mediated inflammation. Rats' carotid artery post-injury media remodeling and neointima development are prevented by inhibiting circulating TNF, but human carotid artery smooth muscle cells invention to TNF by increasing cell proliferation. It has been demonstrated that inhibiting TNF increases endothelium function by promoting the regeneration of endothelial cells. Interleukin-1 beta (IL-1), interleukin-6 (IL-6), TNF, and MCP-1 are vascular inflammatory mediators expressed in endothelial cells and other cell types. NF-B, a pro-inflammatory factor downstream of TNF, controls their expression.[13]

Following vascular damage, activated NF-B promotes the proliferation of vascular smooth muscle cells and is a critical factor in neointima hyperplasia.[14] C-reactive protein is an additional indicator of redness (CRP). The acute-phase response is thought to be typified by CRP, a charity that foretells the risk of cardiovascular events. [14] CRP is also expressed in other cell types, including smooth muscle and the endothelial cells of atherosclerotic arteries. Vascular disease is mediated in part by CRP. Studies conducted in vitro have revealed that CRP upregulates AT1R, impairs endothelial progenitor cell differentiation and function, and has pro-inflammatory and prothrombotic effects.[14-16] Neointima development in damaged arteries is significantly aided by CRP's activation of the classical complement signaling cascade.

RAAS and Vascular Inflammation

Vascular inflammation and remodeling are initiated mainly and maintained by RAAS. Cardiovascular disease

progresses due to impaired endothelial function brought on by vascular inflammation. A defective endothelium is leaky, promotes inflammatory cell migration into the arterial wall, and increases the rapid growth of smooth muscle cells, all of which reduce vascular function and raise the danger of tissue damage and cardiovascular disease. An endothelium that isn't working properly creates an inflammatory environment that encourages the attachment and recruitment of inflammatory cells, which are notorious and designated crucial in the elaboration of atherosclerosis. An association relating high blood pressure to atherosclerosis through Ang II-mediated inflammation is becoming more evident. Acute administration of Ang II in rats significantly increases leukocyte adhesion.[17]

Studies on humans and animals demonstrate that Ang II causes pro-inflammatory reactions in the kidney, heart, and arteries by controlling cytokine and chemokine expression. Ang II activates NF-B and causes the production of IL-6.[18] Atherogenesis is an inflammation-mediated process initiated and progresses due to Ang II. By recruiting inflammatory cells, Ang II creates a positive feedback loop in wounded arteries, producing additional Ang II and vascular inflammation.[19] A strong prooxidant, Ang II. Superoxide anions are produced due to Ang II, and prooxidant NADH/NADPH signaling is also activated. NO protects the cardiovascular and renal systems. Numerous effects of NO on the vasculature include leukocyte adherence to endothelium inhibition, platelet aggregation and adhesion inhibition, and vasodilatation of all types of blood arteries. Additionally, NO reduces oxidative stress and suppresses the proliferation of vascular smooth muscle cells, mitogenesis, and DNA synthesis.[20]

NO bioavailability depends on eNOS activity, and essential Hypertension is linked to decreased eNOS activity. Aldosterone is another hormone that the RAAS uses to mediate its pro-inflammatory and profibrotic effects. Aldosterone causes cardiac fibrosis in conjunction with macrophages and contributes to tissue ischemia and organ fibrosis.[21] Aldosterone influences vascular remodeling, insulin resistance, and atherosclerosis processes. Aldosterone changes insulin signaling in vascular smooth muscle cells by upregulating the IGF1R and hybrid receptors' expression and modifying membrane shape via tyrosine kinase receptors.[22] Rat aorta oxidative stress is induced by chronic aldosterone infusion, and the MR antagonist spironolactone decreases reactive oxygen species production.[23]

RAAS Blockers and Vascular redness

This document aims to discuss the upshots of RAAS blockers on vascular soreness and subsequent cardiovascular events. Recent clinical studies have found that RAAS blockers, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), canister shrink the risk of vascular inflammation and subsequent cardiovascular events. [24] However, the exact mechanisms these drugs reduce inflammatory responses are still largely unknown. This paper will discuss the research available and provide insights into the potential effects of RAAS blockers on vascular inflammation and subsequent cardiovascular events.[25]

The benefits of RAAS blockers in treating vascular inflammation are well-documented. RAAS blockers are a class of drugs that block the action of the renin-angiotensin-aldosterone system, thus preventing the release of vasoconstrictor hormones and decreasing inflammation. In addition, RAAS inhibitors may reduce the risk of developing vascular complications by tumbling inflammation in the affected area. Furthermore, RAAS blockers can help to improve blood flow and reduce oxidative stress, which can help to reduce the risk of stroke and heart attack.[26]

Direct Inhibitors of Renin (DRIs)

By preventing renin's enzyme activity, DRIs prevent RAAS. The oral direct renin inhibitor aliskiren, a recently licensed DRI, reduces blood pressure by obstructing the RAAS's rate-limiting phase. Andersen et al. and others. Aliskiren is well-tolerated by the endothelium. In type I diabetic patients, it enhanced endothelial function without lowering blood pressure.[27] In a transgenic mouse model, aliskiren alone or combined with atorvastatin decreased atherosclerosis onset and progression by decreasing monocyte adhesion and MCP-1 levels.[28]

Potential Inhibitors and the (pro)renin Receptor

Inhibitors of this receptor can be used as therapeutic agents for various disorders, such as Hypertension and diabetes. Recent analyses have indicated that the prorenin receptor is essential for regulating blood pressure and may be a target for new treatments. Various types of inhibitors

can be used to target the prorenin receptor, from small molecules to natural products. Recent analyses have highlighted the prorenin receptor (PRR) potential as a potential renin-angiotensin system (RAS) inhibitor.[29] The RAS is a brigadier hormonal system in mammalian physiology and is labyrinthine in the instruction of cardiovascular and renal functions. PRR is believed to be a key inhibitor of RAS activity, potentially offering novel therapeutic targets for treating Hypertension, stroke and cardiovascular diseases. By binding to PRR, prorenin may be able to reduce the activity of the RAS, leading to decreased blood pressure and improved cardiovascular health.[30]

Inhibitors of the ACEIs

ACEIs have been widely used to treat cardiovascular diseases, Hypertension, cardiac botch, and coronary artery infection. ACEIs inhibit the endeavor of angiotensin-converting enzyme, which is necessary for the production of angiotensin II, an important hormone which regulates blood pressure. By spoiling the realization of angiotensin II, ACEIs reduce blood pressure and improve symptoms of cardiovascular diseases. In addition to their effects on cardiovascular diseases, ACEIs have been shown to have other benefits, such as reducing the gamble of myocardial infarction and fondle.[31]

Angiotensin Receptors Blockers (ARBs):

RAAS blockade with ARBs has proven to improve endothelial function and inflammation. The anti-inflammatory action of ARB candesartan is mediated via calming of the inspiring process toll-like receptors 2 and 4 (TLR2 and TLR4). According to investigations done in vivo and in vitro.[32] TLRs have been linked to the onset and evolution of cardiovascular disease. TLR4 participates in blood pressure control and a slight resistance artery vessel constriction in animal models of Hypertension. Irbesartan, an ARB, has been demonstrated in studies on hypertension patients to lower CRP, ICAM-1, IL- 6, and 8-isoprostane, a measure of levels of oxidative stress, as well as to enhance vascular responsiveness and endothelial function. [33] In mediating endothelial dysfunction, it is inhibited in its function. Both are factors in the development of vascular inflammation and vascular incidents.

Studies conducted in the lab and on animals have revealed that ARB Olmesartan blocks the migration of aortic vascular smooth muscle cells caused by Ang II, preventing vascular remodelling.[34] The use of ARBs in treating atherosclerosis and coronary disease is advantageous. Patients with atherosclerosis and healthy endothelial function benefit from losartan medication regarding flow-mediated coronary artery disease.

Mineralocorticoid Receptor Antagonists (MRA):

Independent of the effects of blood pressure effects of renal MR, dysregulated mineralocorticoid system signaling has an impact on Hypertension, atherosclerosis, and cardiac failure.[35] In patients with cardiovascular disease and danger elements, abnormally activated MR adversely regulates endothelial function. Eplerenone and spironolactone, two commercially available antagonists, are efficient treatments for heart failure with high blood pressure.[36] They work by inhibiting aldosterone actions at the level of MR. MR found in vascular smooth muscle cells, EL cells, and cardiomyocytes mediate the impact of aldosterone on the cardiovascular system. According to studies, MR activation triggers several waving trials in the cardiovascular system along with oxidative stress, inhibits vascular lessening, and results in vascular irritation, fibrosis, and remodelling.[37]

Novel antagonists of the mineralocorticoid receptor:

Since only a few MRA have received clinical approval (spironolactone, eplerenone, and canrenone in the US and Europe), research is now being done to create new MRA. However, only a few newly identified compounds were developed for medical training due to MR structure-based drug design research, which has produced a few new MRA candidates. One of these novel MRAs, PF-3882845, dramatically decreased urine albumin and preserved kidney; these outcomes enabled this novel MRA to be used in ongoing clinical investigations.[38]

The MR binding selectivity of other latest MR antagonists, including dihydrofuran-1-one and dihydropyran-2-one, is highly promising in vitro experiments. However, BR-4628, a novel selective nonsteroidal molecule recently discovered, has demonstrated significant efficacy and discernment on behalf of MR in vivo and in vitro conclusions.[39]

Aldosterone Synthase Inhibitors

The creative substitute method to MRA for limiting the effects of aldosterone is to reduce Aldosterone production

at the enzyme stage, Aldosterone production (AS), CYP11B2. The newest treatment method to minimise aldosterone synthesis is aldosterone synthase inhibitors (ASI).[40] While decreasing Fadrozole 286A (FAD 286A) enhanced plasma renin hobby, cardiac hypertrophy, and cardiac rehab in animal models, which was evidenced by dose-dependently block Ang II Conjugated aldosterone blend in human adrenocortical carcinoma cells.[39]

Revascularization and RAAS

Ang II also causes thrombosis, vessel modification, and plaque rupture. It takes the expression of the fundamental fibroblast growth factor (bFBS), changing development factor-1 (TGF1), and the growth factor insulin (IGF) for Ang II to encourage vascular remodelling.[37] The enhanced migration of vascular cells and altered extracellular matrix composition caused by Ang-II mediated vascular remodeling. Changes in blood artery form and function, particularly in small resistance blood arteries, exacerbate the side effects of high blood pressure. Additionally, tiny blood vessels remodel before left ventricular hypertrophy, thickening of the mediastinum in the carotid arteries, and elevations in microalbuminuria levels. People with Hypertension have tiny resistance arteries with smaller lumens and exterior diameters.[40] Reduced amounts of vasodilators and higher awareness of Ang II and associated routes for transferring signals are linked to changes in tiny arteries' function.

The growth factor Ang II also controls the differentiation, hypertrophy, and death of cells. Vascular smooth muscle cells' multiplying and hypertrophy are the causes of the Ang II-induced remodeling upshots in vascular remodeling. The proliferation versus hypertrophy impacts of Ang II depends on the kind of cell and the genes that control the cell cycle. TGF1-mediated signaling from Ang II causes cardiomyocytes to hypertrophy, and blocking the TGF1 receptor reverses this effect. Cardiomyocytes enlarge as a result of Ang II. [38] Atherosclerosis and post-angioplasty neointima hyperplasia are vascular remodeling diseases where the systemic and local renin-angiotensin systems play a significant role.[41]

References

1. Ferrario CM, Strawn WB. Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. Am J Cardiol. 2006; 98(1):121-8. DOI: https://doi.org/10.1016/j.amjcard.2006.01.059
2. Goldblatt H, Lynch J, Hanzal RF, Summerville WW. Studies on experimental hypertension: The production of persistent elevation of systolic blood pressure by means of renal ischemia. J Exp Med. 1934; 59(3):347-79. DOI: https://doi.org/10.1084/jem.59.3.347
3. Fyhrquist F, Saijonmaa O. Renin-angiotensin system revisited. J Inter Med. 2008; 264(3):224-36. DOI: https://doi.org/10.1111/j.1365-2796.2008.01981.x
4. Nguyen G, Delarue F, Burcklé C, Bouzhir L, Giller T, Sraer JD. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. J Clin Investig. 2002; 109(11):1417-27. DOI: https://doi.org/10.1172/JCI14276.
5. Huang Y, Noble NA, Zhang J, Xu C, Border WA. Renin-stimulated TGF-β1 expression is regulated by a mitogen-activated protein kinase in mesangial cells. Kidney Int. 2007; 72(1):45-52. DOI: https://doi.org/10.1038/sj.ki.5002243
6. Staessen JA, Li Y, Richart T. Oral renin inhibitors. Lancet. 2006; 368(9545):1449-56. DOI: https://doi.org/10.1016/S0140-6736(06)69442-7
7. Gebru Y, Diao TY, Pan H, Mukwaya E, Zhang Y. Potential of RAS inhibition to improve metabolic bone disorders. BioMed Res Int. 2013. DOI: https://doi.org/10.1155/2013/932691
8. Cannavo A, Bencivenga L, Liccardo D, Elia A, Marzano F, Gambino G, et al. Aldosterone and mineralocorticoid receptor system in cardiovascular physiology and pathophysiology. Oxid Med Cell Longev. 2018. DOI: https://doi.org/10.1155/2018/1204598
9. Gustafsson F, Azizi M, Bauersachs J, Jaisser F, Rossignol P. Targeting the aldosterone pathway in cardiovascular disease. Fundam Clin Pharmacol. 2012; 26(1):135-45. DOI: https://doi.org/10.1111/j.1472-8206.2011.01004.x
10. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, et al. A novel angiotensin-converting enzyme–related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res. 2000; 87(5):e1-9. DOI: https://doi.org/10.1161/01.RES.87.5.e1
11. Zhong J, Guo D, Chen CB, Wang W, Schuster M, Loibner H, et al. Prevention of angiotensin II–mediated renal oxidative stress, inflammation, and fibrosis by angiotensin-converting enzyme 2. Hypertension. 2011; 57(2):314-22. DOI: https://doi.org/10.1161/HYPERTENSIONAHA.110.164244
12. Ferrario CM. Angiotensin-converting enzyme 2 and angiotensin-(1-7) an evolving story in cardiovascular regulation. Hypertension. 2006; 47(3):515-21. DOI: https://doi.org/10.1161/01.HYP.0000196268.08909.fb
13. Richard V, Hurel-Merle S, Scalbert E, Ferry G, Lallemand F, Bessou JP, et al. Functional evidence for a role of vascular chymase in the production of angiotensin II in isolated human arteries. Circulation. 2001; 104(7):750-2. DOI: https://doi.org/10.1161/hc3201.094971
14. Tracy RP. Inflammation in cardiovascular disease: cart, horse, or both?. Circulation. 1998; 97(20):2000-2. DOI: https://doi.org/10.1161/01.CIR.97.20.2000

15. Mason RP. Optimal therapeutic strategy for treating patients with hypertension and atherosclerosis: focus on olmesartan medoxomil. Vasc Health Risk Manag. 2011; 24:405-16. DOI: https://doi.org/10.2147/VHRM.S20737
16. Parameswaran N, Patial S. Tumor necrosis factor-α signaling in macrophages. Crit Rev Eukaryot Gene Expr. 2010; 20(2). DOI: https://doi.org/10.1615/CritRevEukarGeneExpr.v20.i2.10
17. Gao X, Belmadani S, Picchi A, Xu X, Potter BJ, Tewari-Singh N. Tumor necrosis factor-α induces endothelial dysfunction in Leprdb mice. Circulation. 2007; 115(2):245-54. DOI: https://doi.org/10.1161/CIRCULATIONAHA.106.650671
18. Pelisek J, Rudelius M, Zepper P, Poppert H, Reeps C, Schuster T, et al. Multiple biological predictors for vulnerable carotid lesions. Cerebrovasc. Dis. 2009; 28(6):601-10. DOI: https://doi.org/10.1159/000247605
19. Russo G, Leopold JA, Loscalzo J. Vasoactive substances: nitric oxide and endothelial dysfunction in atherosclerosis. Vasc Pharmacol. 2002; 38(5):259-69. DOI: https://doi.org/10.1016/S1537-1891(02)00250-1
20. Zimmerman MA, Selzman CH, Reznikov LL, Miller SA, Raeburn CD, Emmick J, et al. Lack of TNF-α attenuates intimal hyperplasia after mouse carotid artery injury. Am J Physiol Regul Integr. 2002; 283(2):R505-12. DOI: https://doi.org/10.1152/ajpregu.00033.2002
21. Fujita M, Shannon JM, Irvin CG, Fagan KA, Cool C, Augustin A, et al. Overexpression of tumor necrosis factor-α produces an increase in lung volumes and pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol . 2001; 280(1):L39-49. DOI: https://doi.org/10.1152/ajplung.2001.280.1.L39
22. Lambert CM, Roy M, Meloche J, Robitaille GA, Agharazii M, Richard DE, et al. Tumor necrosis factor inhibitors as novel therapeutic tools for vascular remodeling diseases. Am J Physiol Lung Cell Mol Physiol . 2010; 299(4):H995-1001. DOI: https://doi.org/10.1152/ajpheart.00562.2010
23. Krasinski K, Spyridopoulos I, Kearney M, Losordo DW. In vivo blockade of tumor necrosis factor-α accelerates functional endothelial recovery after balloon angioplasty. Circulation. 2001; 104(15):1754-6. DOI: https://doi.org/10.1161/hc4001.098046
24. Han Y, Runge MS, Brasier AR. Angiotensin II induces interleukin-6 transcription in vascular smooth muscle cells through pleiotropic activation of nuclear factor-κB transcription factors. Circ Res. 1999; 84(6):695-703. DOI: https://doi.org/10.1161/01.RES.84.6.695
25. Von Känel R, Mills PJ, Mausbach BT, Dimsdale JE, Patterson TL, Ziegler MG, et al. Effect of Alzheimer caregiving on circulating levels of C-reactive protein and other biomarkers relevant to cardiovascular disease risk: a longitudinal study. Gerontol. 2012; 58(4):354-65. DOI: https://doi.org/10.1159/000334219
26. Hurlimann J, Thorbecke GJ, Hochwald GM. The liver as the site of C-reactive protein formation. J Exp Med. 1966; 123(2):365-78. DOI: https://doi.org/10.1084/jem.123.2.365
27. Calabró P, Willerson JT. Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. Circulation. 2003; 108(16):1930-2. DOI: https://doi.org/10.1161/01.CIR.0000096055.62724.C5
28. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation. 2000; 102(18):2165-8. DOI: https://doi.org/10.1161/01.CIR.102.18.2165
29. Verma S, Kuliszewski MA, Li SH, Szmitko PE, Zucco L, Wang CH. C-reactive protein attenuates endothelial progenitor cell survival, differentiation, and function: further evidence of a mechanistic link between C-reactive protein and cardiovascular disease. Circulation. 2004; 109(17):2058-67. DOI: https://doi.org/10.1161/01.CIR.102.18.2165
30. Wang CH, Li SH, Weisel RD, Fedak PW, Dumont AS, Szmitko P, et al. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. Circulation. 2003; 107(13):1783-90. DOI: https://doi.org/10.1161/01.CIR.0000061916.95736.E5
31. Hage FG, Oparil S, Xing D, Chen YF, McCrory MA, Szalai AJ. C-reactive protein-mediated vascular injury requires complement. Arteriosclerosis, Thrombosis, and Vascular Biology. 2010; 30(6):1189-95. DOI: https://doi.org/10.1161/ATVBAHA.110.205377
32. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005; 111(25):3481-8. DOI: https://doi.org/10.1161/CIRCULATIONAHA.105.537878
33. Danesh J, Muir J, Wong YK, Ward M, Gallimore JR, Pepys MB. Risk factors for coronary heart disease and acute-phase proteins. A population-based study. Eur Heart J. 1999; 20(13):954-9. DOI: https://doi.org/10.1053/euhj.1998.1309
34. Tang WB, Zhou YQ, Zhao T, Shan JL, Sun P, Yang TT, et al. Effect of interleukin-6 (IL-6) on the vascular smooth muscle contraction in abdominal aorta of rats with streptozotocin-induced diabetes. Chin J Physiol. 2011; 54(5):318-23. DOI: https://doi.org/10.4077/CJP.2011.AMM069
35. Steiner MK, Syrkina OL, Kolliputi N, Mark EJ, Hales CA, Waxman AB. Interleukin-6 overexpression induces pulmonary hypertension. Circ Res. 2009; 104(2):236-44. DOI: https://doi.org/10.1161/CIRCRESAHA.108.182014
36. Iversen PO, Nicolaysen A, Kvernebo K, Benestad HB, Nicolaysen G. Human cytokines modulate arterial vascular tone via endothelial receptors. Pflügers Archiv. 1999; 439:93-100. DOI: https://doi.org/10.1007/s004249900149
37. Empana JP, Jouven X, Canouï-Poitrine F, Luc G, Tafflet M, Haas B, et al . C-reactive protein, interleukin 6, fibrinogen and risk of sudden death in European middle-aged men: the PRIME study. Arterioscler Thromb Vasc Biol. 2010; 30(10):2047-52. DOI: https://doi.org/10.1161/ATVBAHA.110.208785
38. Niida T, Isoda K, Kitagaki M, Ishigami N, Adachi T, Matsubara O, et al. IκBNS regulates interleukin-6 production and inhibits neointimal formation after vascular injury in mice. Card Res. 2012; 93(2):371-9. DOI: https://doi.org/10.1093/cvr/cvr323
39. Rohde LE, Lee RT, Rivero J, Jamacochian M, Arroyo LH, Briggs W, et al. Circulating cell adhesion molecules are correlated with ultrasound-based assessment of carotid atherosclerosis. Arteriosclerosis, thrombosis, and vascular bioArterioscler Thromb Vasc Biollogy. 1998; 18(11):1765-70. DOI: https://doi.org/10.1161/01.ATV.18.11.1765
40. Neves MF, Amiri F, Virdis A, Diep QN, Schiffrin EL. Role of aldosterone in angiotensin II-induced cardiac and aortic inflammation, fibrosis, and hypertrophy. Can J Physiol Pharmacol . 2005; 83(11):999-1006. DOI: https://doi.org/10.1139/y05-068
41. Pueyo ME, Gonzalez W, Nicoletti A, Savoie F, Arnal JF, Michel JB. Angiotensin II stimulates endothelial vascular cell adhesion molecule-1 via nuclear factor-κB activation induced by intracellular oxidative stress. Arteriosclerosis, thrombosis, and vascular bioArterioscler Thromb Vasc Biollogy. 2000; 20(3):645-51. DOI: https://doi.org/10.1161/01.ATV.20.3.645.