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Blood Pressure-Independent Atherogenic and Thromboembolic Mechanisms of the Renin-Angiotensin-Aldosterone System

K. Lottermoser, H. Vetter, R. Düsing

Numerous studies have provided insight into the possible role of the renin-angiotensin-aldosterone system (RAAS) in the pathophysiology of atherosclerotic vascular disease and its thromboembolic complications. This article reviews mechanisms of the RAAS reaching beyond blood pressure control and extracellular fluid volume regulation which may contribute to the development of cardiovascular disease. In this context, growing evidence supports the concept that angiotensin II mediates key events that lead to progressive atherosclerosis and thromboembolism, including growth and proliferation, impaired fibrinolysis, oxidative stress and inflammation. *J Clin Basic Cardiol 2001; 4: 89–91.*

Keywords: renin-angiotensin system, atherosclerosis, thromboembolism, growth factors, fibrinolysis

Various studies point to a blood pressure-independent relation between activation of the renin-angiotensin-aldosterone system (RAAS) and the development of ischaemic cardiovascular disease such as myocardial infarction and chronic heart failure [1]. Thus, hypertensive patients with high plasma renin activity have been shown to be at higher risk of myocardial infarction than those with low renin activity [2–4]. Also, the deletion polymorphism DD of the angiotensin converting enzyme (ACE) genotype may be associated with higher levels of plasma ACE without an effect on arterial blood pressure. Interestingly, there is evidence for an increased cardiovascular risk in these patients [5, 6]. Furthermore, with the development of ACE-inhibitors it became evident that these drugs reduce coronary ischaemic events which could not be explained by the drugs' haemodynamic effects alone [7]. The underlying pathophysiologic mechanisms of these findings have not yet been completely understood. Experimental evidence suggests that angiotensin II (A II), besides its well-known effects on blood-pressure and extracellular fluid volume, may also affect growth and proliferation of various tissues such as fibroblasts and vascular smooth muscle cells, stimulate extracellular matrix formation by an increased production of collagen and other proteins, increase the adhesion and infiltration of platelets and monocytes, promote oxidative stress, and may be involved in the regulation of fibrinolysis and apoptosis.

Pathophysiologic Aspects of Atherosclerosis

Among other functions, the healthy endothelium possesses vasodilatory and anti-oxidative activity, its surface acts anticoagulatory and it prevents the proliferation of underlying smooth muscle cells as well as the adhesion of circulating blood cells, thus preventing inflammation. Altogether, these mechanisms act against the development of atherosclerotic lesions. Obviously, atherogenesis is a complex and multicausal phenomenon, involving a series of highly specific cellular and molecular responses that can best be described, in aggregate, as an inflammatory disease [8, 9]. The first step in the progression of the atherosclerotic process is endothelial dysfunction, leading to a cascade of local pathologic responses in the arterial wall and finally resulting in the atherosclerotic lesion.

Accumulating evidence suggests that one of the major pathophysiologic mechanisms involved in the pathogenesis of atherosclerosis is enhanced oxidative stress. An important manifestation of this altered redox state is the modulation of a set of proinflammatory genes that are regulated directly or indirectly by reactive oxygen species. Atherogenic stimuli such as hypertension or hypercholesterolaemia appear to activate the inflammatory response by causing expression of mononuclear leucocyte recruiting mechanisms. The gene for one of these, the vascular cell adhesion molecule 1 (VCAM-1), is controlled at least in part by transcriptional factors regulated by oxidative stress. The inflammatory response is thus mediated by monocyte-derived macrophages and specific subtypes of T lymphocytes and it is elicited by an abnormal oxidative metabolism at every stage of the disease [10]. Alterations in the redox state of the arterial wall may also contribute to vascular smooth muscle cell (VSMC) migration and proliferation and the production of extracellular matrix components, contributing to the progress of the inflammatory process [9]. The increased permeability of the endothelium with respect to leucocytes or platelets and a procoagulant property of the endothelium, due to impaired fibrinolysis, are further signs of endothelial dysfunction.

Possible Role of the RAAS in Atherosclerosis

Numerous studies suggest that the the renin-angiotensin system contributes to the pathogenesis of atherosclerosis [11, 12]. A II is now recognized as the central effector hormone in the RAAS-cascade [13]. Tissue ACE and angiotensin II production are increased in atherosclerotic lesions [14, 15]. Since atherosclerosis may occur in the setting of normal or even low arterial blood pressure, this finding cannot be explained by the interrelationship between angiotensin II and blood pressure.

Cytokines

Because chronic inflammation is a hallmark of atherosclerosis, it was suspected that A II may elicit inflammatory signals, such as cytokines. Recent data also suggest that inflammatory cells may be capable of producing A II, therefore creating the potential for a vicious cycle in vascular lesions where there is inflammation, angiotensin formation, lesion formation, and progression of disease [16]. Thus, local production of A II together with circulating A II may be particularly important in the progression of an atherosclerotic lesion.

Although the separate roles of A II and cytokines in atherosclerosis have been well established [17–19], the role of A II in cytokine production has just recently been explored

[20]. Cytokines serve as growth factors and/or differentiation factors, such as inflammatory mediators. Excreted by macrophages, interferones, interleukines and transforming growth factor-beta (TGF-β) act as inhibitors of proliferation. In fact, A II can induce the expression of inflammatory genes, such as VCAM-1 [11]. VCAM-1 plays a major role in monocyte adhesion to endothelial cells [21] and in the regulation of VSMC growth. In rats made hypertensive by A II infusion, monocytes predominantly infiltrate endothelial cells [22]. Monocyte infiltration into the vessel wall, which is a key initial step in the process of atherosclerosis, is mediated in part by monocyte chemoattractant protein-1 (MCP-1). Rat VSMC treated with A II exhibit a dose-dependent increase in MCP-1 mRNA expression that is prevented by the angiotensin II type 1 (AT_1) receptor antagonist losartan. A II may thus promote atherogenesis by direct activation of MCP-1 gene expression in vascular smooth muscle cells [23].

A II increases the expression of interleukin-6 (IL-6) mRNA and protein, which is a multifunctional proinflammatory cytokine, in a dose-dependent manner via activation of the AT_1 receptor [12, 20, 24]. This effect is completely blocked by an AT_1 receptor antagonist [20].

The expression of VCAM-1 by human endothelial cells is stimulated by cytokines such as IL-1. This process is mediated by redox-sensitive control mechanisms [25]. In a recent study by Nakamura et al. A II did not have an effect on tumour necrosis factor-α (TNF-α) secretion and gene transcription in rat renal resident macrophage cells [24].

There is evidence that ACE inhibitors could counteract atherogenesis by reducing the induction of several cytokines by A II or by abolishing A II induced expression of their receptors [26].

Oxidative Mechanisms

A II can induce oxidative stress in the vasculature via generation of free oxygen radicals [27, 28]. The destruction of endothelium-derived NO by excessive production of oxygen-free radicals impairs the ability of the endothelium to preserve endothelial integrity. Moreover, enhanced activity of the RAS (angiotensin-I converting enzyme) increases breakdown of bradykinin, thus decreasing the release of NO. These and other changes [29] may act to depress NO availability. As NO inhibits the A II-promoted monocyte adhesion to the vessel wall, reduces smooth muscle cell proliferation, and prevents platelet aggregation, which are all important steps in the atherogenic process, NO may indeed play a crucial role in the progression of the early atherosclerotic lesion.

ACE inhibitors reduce atherosclerotic lesions in several animal models [30–32]. They can protect the endothelium in two ways: they inhibit the production of A II, thus preventing oxidative stress and therefore the oxidation of NO and they inhibit kinin metabolism meaning more bradykinin activating NO.

The signalling pathways involved in the long-term metabolic effects of A II in VSMC are incompletely understood but include the generation of molecules likely to affect oxidase activity. Griendling et al. observed that A II specifically activates both the NADPH- and NADH-dependent oxidases which promote superoxide anion generation [27]. As determined by isometric vascular tension studies, A II-mediated superoxide-production may also play a crucial role in the early stage of atherosclerosis [33].

VSMC Growth and Proliferation

Increased vascular smooth muscle cell growth is another common feature in the pathogenesis of atherosclerosis. The growth of VSMC is controlled to an important extent by the endothelium [34]. Dysfunctional endothelium may contribute to or permit VSMC growth and/or proliferation, which contributes to the narrowing of the arterial lumen. A II causes rapid induction of the growth-associated immediate early gene expression by mitogen-activated protein kinase (MAPK) pathways [35]. It induces profibrogenic TGF-β transcription and synthesis and upregulates TGF-β receptor type II expression in cultured murine proximal tubular cells [36]. A II is a potent hypertrophic and anti-apoptotic factor for VSMC and it activates endothelin which is another vasoconstrictor and promoter of proliferation. It is suspected that A II is responsible for activating the expression of positive and negative cytokine gene networks in VSMC [37].

Apoptosis

Most of the known effects of angiotensin II can be attributed to the AT_1 receptor and are therefore antagonized by specific AT_1 receptor antagonists [30, 38]. Thus, experimental studies with various AT_1 receptor antagonists in a variety of tissues such as isolated cardiomyocytes, endothelial cell cultures, coronary endothelial cells and fibroblasts have demonstrated that these agents inhibit the growth promoting and proliferative effects of A II [39–44]. Recent experimental studies suggest that A II may mediate an antiproliferative effect and apoptosis via the AT_2 receptor [45, 46]. Interferon regulatory factor I (IRF-1) upregulates the AT_2 receptor in apoptotic cells, suggesting that the cytokines may play an important role in angiotensin regulated apoptosis. An AT_2-mediated apoptotic effect of A II is clearly demonstrable in transfected rat VSMC and rat cardiomyocytes (cytomegalovirus vector) [47]. Conversely, an AT_1-mediated antiapoptotic effect was demonstrable in similar cells. Thus, cytokines obviously modulate effects of A II by regulating A II receptor subtypes.

Fibrinolysis

Experimental and clinical studies have provided support for a role of the endogenous RAAS in regulating the fibrinolytic system which is another factor involved in the pathogenesis of atherothromboembolic disease. The main determinants of vascular fibrinolytic balance are tissue plasminogen activator (t-PA) and its specific inhibitor plasminogen activator inhibitor-1 (PAI-1). While bradykinin promotes the release of the profibrinolytic t-PA, angiotensin II may stimulate PAI-1 *in vitro* [48, 49] and *in vivo* [50, 51]. The serum concentration of PAI-1 correlates with plasma renin and aldosterone [52]. Increased PAI-1 expression together with lower levels of t-PA are characteristic of advanced atherosclerotic lesions [53, 54].

Conclusion

The RAAS has atherogenic and thromboembolic potential which is evolved by its interaction with cytokines and the fibrinolytic system as well as the induction of cell growth and oxidative stress. Recent studies suggest that A II is the responsible factor related to the involved mediators such as PAI-1, cytokines and free oxygen radicals. The impact of the RAAS in this context is underlined by antiatherogenic effects of ACE-inhibitors in experimental studies and the reduction in cardiovascular events and mortality in patients treated with inhibitors of the RAAS.

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