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Chapter 7

The Role of Renin-Angiotensin System in Ocular Inflammation and Uveitis

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Abstract

The renin-angiotensin system (RAS) plays an important role in the pathogenesis of inflammation and autoimmune dysfunction. Uveitis is a sight-threatening intraocular inflammatory disorder caused by infectious agents, autoimmune mechanisms, exposure to toxins and many other unknown factors. Most components of RAS have been identified in every organ including the eye. The tissue-specific RAS is believed to exert diverse physiological effects locally independent of circulating angiotensin II (AT II) which functions as the effector arm of RAS causing potent proinflammatory responses via Angiotensin type 1 receptor (AT1R). AT II mediated stimulation of tissue factor (TF), the principal initiator of the clotting cascade and a major regulator of haemostasis and thrombosis rapidly inducible by inflammatory agents in several cell lines including monocytes. Activation of NFκB, a key redox-sensitive transcription factor encoding for the TF gene, plays a key role in that mechanism amplified by locally synthesized angiotensin I. (AT I) The second arm of RAS establishes systemic and local protective axis against inflammation and autoimmune dysfunction via angiotensin-converting enzyme 2 (ACE2) which is a zinc-metallopeptidase able to cleave AT II to form angiotensin-(1–7) [AT-(1–7)]. AT-(1–7), a biologically active peptide, binds to a G-protein coupled receptor Mas, and activates signaling pathways that counteract the effects of AT II by negatively effecting inflammatory responses and negatively modulating leukocyte migration, cytokine expression and release, and fibrogenic pathways. The purpose of this chapter is to analyze both pro-inflammatory and protective role of RAS in ocular inflammation and uveitis both in humans and experimental models.

Keywords: uveitis, renin, angiotensin, angiotensin converting enzyme, tissue factor

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1. Introduction

The renin-angiotensin system (RAS) is a hormone system playing an important role in the pathogenesis of inflammation and autoimmune dysfunction [1]. RAS pathway elements are produced intrinsically in many diverse tissues, including the retina for controlling local inflammatory responses and maintaining local homeostasis [1]. While RAS is important for controlling normal inflammatory responses, hyperactivation of this pathway is disclosed to potentiate oxidative stress and inflammatory responses by the activation of nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidases [2]. The tissue-specific RAS is believed to exert diverse physiological effects locally independent of circulating angiotensin II (AT II), which functions as the effector arm of RAS causing potent pro-inflammatory responses via angiotensin type 1 receptor (AT1R) [1]. AT II is considered to stimulate tissue factor (TF), which induces synthesis of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in several cell lines including monocytes [3]. The second arm of RAS is considered to establish systemic and local protective axis against inflammation and autoimmune dysfunction via angiotensin-converting enzyme 2 (ACE2), which cleaves AT II to angiotensin-(1–7) [2]. AT (1–7) is reported to counteract the effects of AT II by negatively affecting inflammatory responses, negatively modulating leukocyte migration, cytokine expression and release, and fibrogenic pathways [2].

Uveitis is considered as an intraocular inflammatory disorder caused by infectious agents or autoimmune mechanisms [4]. The purpose of this chapter is to analyze both pro-inflammatory and protective role of RAS in ocular inflammation and uveitis both in humans and experimental models.

2. RAS as an inflammatory cascade

Renin is considered to cleave angiotensinogen to AT1 that is further processed by ACE/ACE2 to different AT cleavage products including AT II, which is regarded as a principle effector molecule of the RAS [3]. The major functions of AT II are reported to be mediated by AT1R, which is considered to activate directly the key signaling pathways for cell growth and hypertrophy [4]. AT1R has been also shown to activate NF-κB and activator protein 1 (AP-1) to initiate the transcription of multiple proinflammatory genes [4]. AT II is disclosed to activate epidermal growth factor receptors (EGFR) to induce fibronectin synthesis and transforming growth factor beta (TGF-β) activity to promote fibrosis and extracellular matrix formation [3]. The effects of circulating and tissue RAS are considered to be controlled with RAS inhibitors, which prevent not only hypertension but also protect tissues against injury by limiting the potency of deleterious inflammatory responses [3].

Recently, several studies have revealed that modulators of the RAS-including ACE inhibitors or AT1R antagonists display beneficial effects in the treatment of cardiovascular diseases, atherosclerotic, neurodegenerative, autoimmune, and inflammatory diseases [5–8].

3. Angiotensin II and autoimmunity

The modulatory effect of AT II on T-cell responses in autoimmune diseases has been disclosed by a recent study [9]. The effect of AT II in the development of Th1/Th17-mediated multiple sclerosis (MS) has been disclosed in experimental autoimmune encephalomyelitis (EAE)[10]. Elevated levels of AT II, IFN-γ, and IL-17 cytokines have been shown in the peripheral $CD4^+$T cells from EAE mice [10]. AT1R is also considered to involve in experimental autoimmune uveitis (EAU) and experimental autoimmune myocarditis (EAM) through its effect on T-cell function [11]. A recent study has highlighted the role of AT1R in glomerular inflammation associated with autoimmune disease in mice leading to the inflammation resembling human systemic lupus erythematosus [12]. AT1R has also been disclosed in the pathogenesis of myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (MOG-EAE) [13]. The expression of renin, ACE, and AT1R has been shown to be upregulated in macrophages, DCs, and T cells during the course of the MOG-EAE [13].

4. Angiotensin II promotes inflammation and tissue injury

Inflammatory process is considered to involve activation of the endothelium of blood vessels and expression of diverse endothelial cell selectins that have been shown to lead the extravasation of specific leukocyte populations to the site of injury [14].

The expression and secretion of vascular endothelial growth factor (VEGF) by RAS and AT II have been disclosed to increase local vascular permeability [14]. AT II has also been disclosed to promote endothelial dysfunction through COX-2 activation, which generates vasoactive prostaglandins and reactive oxygen species (ROS) [15]. AT II is considered to favor the recruitment of infiltrating inflammatory cells into tissues by stimulating the production of specific cytokine/chemokines. AT II has been shown to induce the production of the potent monocyte chemoattractant MCP-1 in cultured monocytes [15]. Elevated levels of AT II associated with increased expression of MCP-1 and C–C chemokine receptor, CCR2, have been disclosed in the aorta of spontaneously hypertensive rats [16]. Modulation of MCP-1/CCR2 via AT1R blockade has been revealed to reduce vessel inflammation in hypertensive rats [16]. AT II-induced macrophage infiltration in the arterial wall was shown to be virtually absent in CCR2-deficient mice [16]. In models of progressive nephropathies, interstitial accumulation of macrophages was shown to be accompanied by increased renal expression of MCP-1, and renoprotection was provided by the ACE inhibitor lisinopril, which was considered to reduce MCP-1 expression and control inflammation [17]. Dendritic cells (DCs) and highly specialized antigen-presenting cells (APCs) were considered to mediate the pro-inflammatory activity of AT II [18]. Cultured DCs have been shown to express both AT II receptors and AT II, which were considered to enhance DCs migration, maturation, and antigen presenting ability [18]. Recent study in rats with subtotal renal ablation has disclosed blockade of AT II synthesis and its biological activity that resulted in reduction of local DC accumulation and attenuation of

tubulointerstitial damage [19]. In another study considering cultured mesangial and vascular smooth muscle cells, AT II via AT1R signaling was shown to stimulate TLR-4 expression that was considered to promote cellular oxidative injury, apoptosis, and inflammation [20]. T cells were considered to show the pro-inflammatory effects of AT II via AT1R and endogenous RAS, which has been disclosed to modulate T-cell proliferation, cytoskeletal rearrangements, migration, and release of specific cytokines and chemokines [20].

5. Angiotensin II: role in immunosenesence

AT II is considered to stimulate the production of molecular oxygen species that trigger mitochondrial dysfunction and cellular injury [21]. AT II via AT1R stimulation has been shown to activate NAD(P)H oxidase to produce ROS, resulting in oxidative stress damage [21]. It has been proposed that ROSs are the most prominent molecular species involved in the aging process [22]. ROSs have been revealed to contribute significantly to various age-associated organ failures, including hypertension, cardiovascular diseases, and renal damage [22]. Hence, AT II is considered to be involved in organ senescence related to its ability to mediate the release of oxidant species [23]. Recent studies have disclosed that AT II-induced ROS production leads to functional and structural changes of blood vessels that result in vascular senescence and age-related vascular diseases [23]. Previous studies related to the long-term effects of AT II inhibition by either ACEi or ARBs disclosed protective effects on the cardiovascular system of rats and revealed the prolongation of the life span of rats [24, 25]. Another study disclosed that old mice lacking AT1R did not develop age-related cerebral circulation damage caused by the accumulation of oxygen radicals [26]. The inhibition of RAS has been disclosed to reverse age-related advanced myocardiac hypertrophy and fibrosis in old hypertensive rats, and the protective effect presumably was considered to involve the suppression of AT II-mediated oxidative stress, as disclosed by reduced expression of NAD(P)H oxidative components in the hearts of aged rats [26].

6. Further mechanisms of angiotensin II-induced inflammation: human T and natural killer cells

Co-stimulatory effects of angiotensinogen, AT I, and AT II on the proliferation of T and NK cells have been revealed [27]. T and NK cells were considered to have RAS elements, and they have been synthesizing AT II at the sites of inflammation creating a potential inflammatory amplification system [27, 28]. Th1 immune response has been disclosed to be crucial in the pathogenesis of inflammatory vascular diseases [28].

However, the interaction of AT II with Th1/Th2 cytokines during the development of inflammation is considered debatable. Recent studies have demonstrated the presence of RAS elements in human T and NK cells that they were capable to synthesize their own AT II [29]. Renin-induced inflammation has been related to the binding of AT II to the renin receptor in T cells, NK cells, and DC [29]. AT 2R which was previously considered to antagonize the actions of the AT1R and having beneficial effects in hypertension, cell growth, vascular remodeling, proliferation, and

inflammation, currently, it has been thought to orchestrate the collective recruitment of leukocyte subsets to the sites of inflammation through mediating the effect of AT II [29, 30].

7. Clinical implications

New medical applications of RAS antagonists as anti-inflammatory and immunomodulatory agents without significant side-effects are being considered in the treatment of autoimmune diseases [31, 32].

7.1. Captopril suppresses inflammation in endotoxin-induced uveitis in rats

It has been suggested that ACEi captopril has a strong anti-ocular inflammatory effect in endotoxin-induced uveitis (EIU) [33]. Captopril has been shown to suppress the NF-κB activation in the iris and ciliary body cells by inhibiting the production of AT II [34]. The inhibitory effect of captopril on leucocyte infiltration, protein leakage, and other inflammatory markers in the aqueous humor including TNF-α, PGE-2, MCP-1, NO have also been revealed [35].

TNF-α is an inflammatory cytokine, which plays an important role in the recruitment of inflammatory cells, synthesis of other inflammatory cytokines, eicosanoids, and NO [35]. Anti TNF-α therapy has been used for the treatment of Behcet's disease [36]. The transcription of TNF-α was shown to be under the control of NF-κB [35, 36]. It has previously been disclosed that ACE inhibitors suppress TNF-α synthesis *in vivo* and *in vitro* and captopril was shown to successfully down regulate TNF-α in the aqueous humor by interfering the positive loop between TNF-α and NF-κB [36]. PGE2 and NO in the aqueous humor were considered to have profound effects on local inflammatory processes mainly by increasing vascular permeability and breaking down the blood-aqueous barrier in uveitis [37]. Their concentrations in the aqueous humor were disclosed to be down-regulated by captopril treatment [37]. Inhibition of both TNF-α and PGE2/NO pathways by captopril has been shown to improve EIU in rabbits [38]. Another inflammatory marker MCP-1, which is under NF-κB control, is considered as an important mediator of monocyte infiltration. MCP-1 has been shown to be over expressed in human eyes during acute anterior uveitis as well as in the rat EIU model [38]. The results of the recent studies have disclosed that captopril successfully down-regulated MCP-1 levels in anterior chamber, and it showed its anti-inflammatory properties by affecting monocyte recruitment in EIU in rats [34, 37, 38].

The beneficial effect of AT II blockers on tissue inflammation was also considered to be related to the blockage of Ang II-mediated activation of Toll-like receptors (TLRs) [39]. Drugs that limit AT II synthesis and its biological activity, ACEi lisinopril, or ARB Candesartan were disclosed to result in the suppression of Th1 and Th17 cytokine release and the induction of powerful antigen-specific regulatory T cells (Treg) through the modulation of the NF-κB pathway [40]. Administration of ARB was disclosed to suppress EAU and reduce the severity of myocardial lesions in EAM by inhibiting antigen-specific T-cell activation and contributing to the shift of Th1–Th2 immune response [41]. Chronic treatment with ACEi or ARB has been shown to reduce kidney damage associated with age, and the beneficial effect of RAS inhibition was

considered to be related to the preservation of renal mitochondria [40]. Enalapril and losartan treatments have been shown to prevent the age-associated decline in the renal mitochondrial capacity for energy production and to attenuate the age-associated increase in mitochondrial oxidant production [40]. RAS inhibition was disclosed to exert a similar protective effect in the liver from aged rats through the maintenance of an adequate mitochondrial function by enhancing expression of genes responsible for mitochondrial respiration and biogenesis [41]. Aging is considered to be the result of chronic inflammation, and the use of RAS inhibitors or genetic deletion of AT1R was considered to extend the life span [41].

7.2. Oral delivery of ACE2/Ang-(1–7) bioencapsulated in plant cells protects against experimental uveitis and autoimmune uveoretinitis

Improving the systemic and local activity of the protective axis of the RAS by oral delivery of ACE2 and Ang-(1–7) bioencapsulated in plant cells has been considered as a therapeutic option for the ocular inflammation. Increased levels of ACE2 and Ang-(1–7) were observed in the retinal circulation after oral administration of ACE2 and Ang-(1–7) expressing plant cells [42]. Oral feeding of mice with bioencapsulated ACE2/Ang-(1–7) was shown significantly to reduce the incidence of EIU [42]. Treatment with bioencapsulated ACE2/Ang-(1–7) in mice disclosed dramatical decrease of cellular infiltration and retinal vasculitis in EAU [42]. It has been concluded that enhancing the protective axis of RAS by oral delivery of ACE2/Ang-(1–7) bioencapsulated in plant cells provide an innovative, highly efficient, and cost-effective therapeutic strategy for ocular inflammatory diseases [42].

8. Conclusions

Hyperactivity of the RAS resulting elevated AT II might contribute to all stages of inflammatory responses including ocular inflammation. ACE2 is more likely to establish a protective axis of RAS involving ACE2/Ang-(1–7)/Mas, which counteract the proinflammatory and hypertrophic effects of the ACE/AngII/AT1R axis. AT II might have also co-stimulatory effects on T cells, NK cells, and DC, which have specific elements of the RAS. RAS antagonists might be used in conjunction with other anti-inflammatory agents as therapy for common diseases in which inflammation plays a major pathogenic role.

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