Drugs of the Future 2010, 35(5): 393-398

CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.5.1484388

REVIEW ARTICLE

COMPOUNDS ACTING ON THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM AS POTENTIAL REGULATORS OF AUTOIMMUNE NEUROINFLAMMATION

D.-H. Lee, R. Gold and R.A. Linker

Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Gudrunstrasse 56, 44791 Bochum, Germany

CONTENTS

SUMMARY

In recent years, an increasing body of evidence has shown that the renin–angiotensin–aldosterone system (RAAS) may play a crucial role as a mediator of cardiovascular and renal morbidity and in vascular inflammation. However, inhibition of the RAAS at different levels may also influence autoimmune responses and modulate T-cell and antigen-presenting cell function, probably via different signaling pathways. In particular, the RAAS may play a role in autoimmune demyelination of the central nervous system, as well as the peripheral nervous system. Thus, modulation of the RAAS, for example inhibition of renin or angiotensin-converting enzyme, as well as blockade of angiotensin II AT_1 receptors, may represent an innovative therapeutic strategy in multiple sclerosis or other autoimmune diseases, as shown in experimental autoimmune encephalomyelitis.

INTRODUCTION

In the last decades, several immunological studies revealed that not only classical components of the immune system, such as T cells, B cells and different cell types of the innate immune system, including antigen-presenting cells (APCs), regulate immune responses. Rather, a variety of different cell types and tissues may play an important role in these processes. In addition to cytokines, chemokines and different immune cell receptors, as well as neurotrophins, different hormones and other mediators are involved in the regulation of immune cell function. In this context, investigating the role of the renin–angiotensin–aldosterone system (RAAS) in inflammation is an area of growing interest. In particular, inhibition of classical RAAS signaling pathways promotes anti-inflammatory effects. This observation may boost further research to test whether modulation of the RAAS may be a suitable target for the therapy of different autoimmune diseases. Here we review the effects of RAAS components on immune responses, with a special focus on neuroinflammatory processes, especially the inflammatory demyelinating disease multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE).

Correspondence: De-Hyung Lee, MD, Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Gudrunstrasse 56, 44791 Bochum, Germany. E-mail: dehyunglee@yahoo.de.

FUNCTION OF THE RAAS

The RAAS plays a crucial role in fluid homeostasis and has been studied for more than a century. In RAAS signaling pathways, renin mediates the proteolysis of angiotensinogen to angiotensin I, which is further processed by angiotensin-converting enzyme (ACE) or angiotensin-converting enzyme 2 (ACE2, ACEH) into different cleavage products, among them angiotensin II (Ang II) (1). Ang II exerts its various actions on several target organs, including the heart, kidney and blood vessels, and thus contributes to many physiological functions, such as regulation of blood pressure or electrolyte homeostasis (2). Ang II mediates its effects by at least two different types of receptors, which have been pharmacologically identified and cloned: the Ang II type 1 receptor (AT_1) and the Ang II type 2 receptor (AT_2). In mice, effects on the AT_1 receptor can be further subdivided and Ang II may interact with AT_{1a} or AT_{1b} receptors.

Moreover, Ang II activates the mineralocorticoid hormone aldosterone from the cortex of the adrenal gland, which plays an important role in salt and fluid homeostasis (3). A further level of complex-

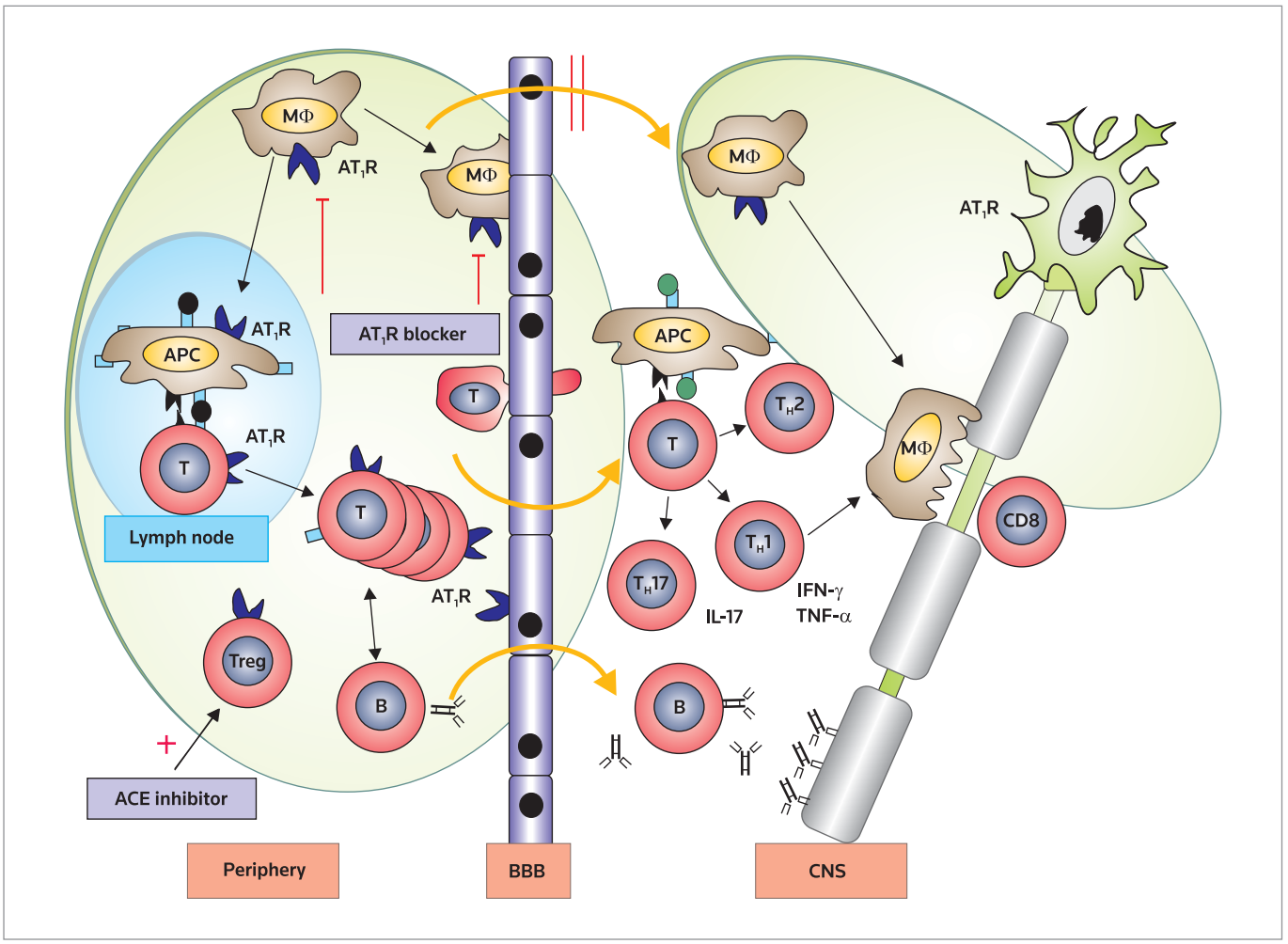

Figure 1. Figure depicting the role of the renin–angiotensin–aldosterone system (RAAS) in autoimmune demyelination. In the periphery, antigen-presenting cells (APCs) prime T cells (T), which are activated and gain the ability to cross the blood–brain barrier (BBB). In the central nervous system (CNS), they initiate an inflammatory cascade, ultimately leading to activation of B cells (B) and macrophages (MΦ), as well as $CD8^+$ T cells (CD8), which cause demyelination or axonal damage. Possible targets of RAAS inhibition in the immune system, including MΦ or regulatory T cells (Treg), are indicated in red. AT_1R, AT_1 receptor.

ity is introduced by the identification of alternative RAAS signaling pathways which may involve ACE2 and further Ang cleavage products like Ang-(1-7) or Ang IV (4).

Ang II enhances the release of catecholamines from the medulla of the adrenal gland and also from nerve terminals. It increases thirst and promotes salt retention, as well as vasoconstriction, thereby significantly contributing to the development of hypertension (2). In vascular disease, Ang II promotes the development of atherosclerosis, providing a first link between the RAAS and the immune system. In atherosclerosis, the pathogenic role of Ang II has been linked to signaling via inflammation-regulating chemokines such as monocyte chemoattractant protein 1 (MCP-1) and its receptor CCR2 (5, 6). Indeed, atherosclerosis may be viewed as a chronic inflammatory disease with an adaptive immune response to the atherosclerotic plaque, as well as associated antigens, including heat shock protein HSP60, oxidized low-density lipoprotein (oxLDL) or ACE itself (7). At early stages of atherosclerosis, "Th1"-polarized $CD4^+$ cells producing interferon gamma (IFN-γ) and other proinflammatory cytokines also contribute significantly to the pathogenesis of the disease (8).

THE RAAS AND IMMUNE RESPONSES

Many aspects point to the fact that there is an intricate interplay between the RAAS and the regulation of immune responses or inflammatory processes (Fig. 1). For example, studies in RAG-1-deficient mice highlight the role of T cells in the pathogenesis of Ang II-induced hypertension and vascular dysfunction (9). Furthermore, *Ace2* knockout mice are characterized by severe cardiac dysfunction associated with the accumulation of cardiac Ang II and, depending on the genetic background, higher blood pressure (10). These changes in *Ace2* knockout mice are associated with enhanced cytokine and chemokine expression and leukocyte infiltration in the heart and cardiomyopathy (11). Additionally, recent studies have

shown that Ang-(1-7), the downstream peptide of ACE2 signaling pathways, is itself an active metabolite of the RAAS and activates its own receptor, known as Mas, which has been characterized as a physiological antagonist of the AT_1 receptor in cardiovascular models (12-14). Thus, treatment with Ang-(1-7) may ameliorate experimental heart failure, diabetic heart failure and endothelial dysfunction in vivo (4, 15, 16). In hypertensive rats, immunosuppressive treatment with dexamethasone protects against Ang II-induced renal damage (17).

In humans, the relevance of Ang II for inflammatory responses was recently shown in kidney transplant patients. Here, the presence of AT_1 receptor-activating antibodies is associated with allograft rejection, and the transfer of human AT_1 receptor antibodies into rodents induces vasculopathy and hypertension in a rat kidney transplant model (18). In clinical trials, modulators of the RAAS, including ACE inhibitors such as captopril, ramipril or lisinopril, display beneficial effects in the treatment of hypertension, kidney disease (including lupus nephritis), myocardial infarction, as well as stroke, and thus are widely used in clinical practice. A similar approach is the pharmacological blockade of the AT_1 receptor, e.g., by candesartan or losartan, which, in contrast to other AT_1 receptor blockers like telmisartan, do not display additional peroxisome proliferator-activating receptor (PPARγ) agonist effects (19).

MULTIPLE SCLEROSIS AND ANIMAL MODELS

Multiple sclerosis (MS) is the most common chronic neurological disease in young adults, affecting predominantly women, with a ratio of about 3:2. Characteristic early symptoms of relapsing–remitting disease courses include sensory disturbances or optic neuritis, while motor impairment may lead to significant disability in progressive MS courses at later disease stages. The last 15 years witnessed the introduction of disease-modifying therapies especially for early phases of the disease. However, their efficacy is still incomplete and there is as yet no cure for this devastating disease.

A complex interplay of genetic as well as environmental factors may contribute to the presumably autoimmune pathogenesis of MS, but the exact etiology of the disease is still unclear. The classic histopathological features of MS lesions comprise inflammation, demyelination and gliosis in the white matter, while more recent investigations have also focused on the pathology of the grey matter (20). In the past 10 years, several studies revealed the importance of degenerative features with axonal injury, as well as loss of axons and probably also neurons, especially for the development of permanent disability (21). The disease course and also the histopathological features of MS can be mimicked in several animal models, the most important being experimental autoimmune encephalomyelitis (EAE) (22).

EAE can be induced in susceptible animals, mostly inbred rodent strains, by immunization with whole central nervous system (CNS) myelin or distinct (myelin) antigens in adjuvant. Over the past decades, experimental studies identified encephalitogenic epitopes of several potential autoantigens, such as myelin oligodendrocyte glycoprotein aa 35-55 (MOG35-55) or proteolipid protein aa 139-151 (PLP139-151). The immunization of susceptible mouse strains such as C57BL/6 mice with MOG or SJL mice with PLP peptide is able to mimic distinct aspects of MS. In particular, the induction of MOG-EAE in the C57BL/6 mouse results in a first relapse followed by a chronic disease phase characterized by demyelination and also degenerative features (23). While much work in these models led to the characterization of major players involved in immune pathogenesis, including pathogenic "Th1/Th17" immune responses or also regulatory elements, fewer studies addressed the role of neurohormones or neuropeptides in these processes. Here, the RAAS may be of special interest given its various interactions with neuronal and also glial cells. In recent years, it has become increasingly clear that the RAAS may not only influence immune reactions in the cardiovascular system or hormonal processes in the CNS, but also immune responses in the nervous system (see below).

ROLE OF THE RAAS IN NEUROINFLAMMATION

In the treatment of cardiovascular diseases via RAAS blockade, the specificity of beneficial anti-inflammatory effects is difficult to delineate since concomitant effects on blood pressure cannot be excluded. However, the role of the RAAS was also investigated during autoimmune demyelination, where blood pressure is not altered. A model for autoimmune demyelination is MOG-EAE in C57BL/6 mice, which mimics many aspects of MS (22, 24). In particular, MOG-EAE is characterized by proinflammatory "Th1" as well as "Th17" T-cell responses and also infiltration of macrophages, as well as a critical role for APC populations, such as dendritic cells (DCs).

Recent studies showed that RAAS peptides are present in CNS lesions of MS patients and that the AT_1 receptor is upregulated in MS plaques, as revealed by immunohistochemistry. In active lesions, AT_1 receptor expression is concentrated in perivascular cuffs. Moreover, expression of the AT_1 receptor was found in endothelial cells, astrocytes and axons (25, 26). These observations led to the conclusion that the existence of crucial RAAS components at the site of active disease in MS may be linked to a functional implication of the RAAS in neuroinflammation. Well in line with this idea, previously published studies in animal models already revealed that treatment with the ACE inhibitor captopril provided beneficial effects in MBP-EAE of the Lewis rat, while a more recent study showed that the AT_1 receptor blocker telmisartan suppressed experimental autoimmune uveitis, a T-cell-mediated disease of the eye (27, 28). In these models, immunological studies pointed to an effect of both compounds on the T-cell response. However, telmisartan also possesses a PPARγ agonist effect which somehow limits the specificity of these findings for the RAAS (19).

Recently, it was also shown that the RAAS influences autoimmune demyelinating processes in the peripheral nervous system. In an animal model of experimental autoimmune neuritis (EAN), the ACE inhibitor captopril improved clinical signs of the disease and reduced inflammatory infiltration in the nerve. In particular, captopril may attenuate the overexpression of matrix metalloproteinases MMP-2 and MMP-9, which are strongly associated with tissue damage. Here, MMPs mediate the proteolysis of β-dystroglycan (β-DG), which belongs to the stabilizing DG complex localized on the outer membrane of Schwann cells, thus promoting demyelination. Consequently, inhibition of MMP by captopril may not only reduce inflammation but also directly interfere with demyelination, and thus may represent a new therapeutic option in autoimmune neuritis (29).

In MOG-EAE, immunized mice displayed increased renin activity. Moreover, RT-PCR analyses revealed an increased expression of AT_{1a} and AT_{1b} receptors, as well as ACE, in components of the immune system. These effects could be downregulated after application of the AT_1 receptor blocker losartan. Upon a closer look, components of the RAAS were differently expressed in distinct immune cell subsets under inflammatory conditions. In peritoneal macrophages, the expression of AT_{1a} and AT_{1b} receptors, as well as ACE and ACE2, was upregulated, whereas the expression of the AT_{1a} receptor was downregulated after application of AT_1 receptor blockers. In T cells, the expression of AT_{1a} and AT_{1b} receptors was increased, while ACE and ACE2 expression was suppressed. During maturation of DCs, both AT_{1a} and AT_{1b} receptors were upregulated (24).

Treatment with the renin inhibitor aliskiren or with the ACE inhibitor enalapril, as well as with the AT_{1a} and AT_{1b} receptor blocker losartan, ameliorated the disease course of MOG-EAE, thus further pointing to a proinflammatory role of classical RAAS pathways in neuroinflammation. Well in line with this idea, histopathological analyses after RAAS blockade revealed a reduced infiltration of macrophages/microglia in the acute and chronic phase of MOG-EAE. Blood pressure-related effects were excluded by treatment with vasodilators, which do not display such immunomodulatory effects in EAE (24).

The development of autoimmune responses in EAE may depend on myelin-specific IFN-γ-producing "Th1" cells, as well as on a more recently described subset of $CD4^+$ T cells that are characterized by the secretion of the interleukin IL-17, i.e., "Th17" cells (30-32). In PLP139-151-immunized mice, pretreatment with the ACE inhibitor lisinopril or the AT_1 receptor antagonist candesartan led to a suppression of "Th1 and "Th17" cytokines, and subsequently to an increase in immunomodulatory mediators such as IL-10 and transforming growth factor-β (TGF-β) (26). Furthermore, adoptive transfer experiments revealed that the proinflammatory phenotype of antigen-specific T helper cells is downregulated after treatment with lisinopril. Finally, the blockade of ACE with lisinopril induced FOXP3-positive regulatory T cells (Treg), which protected PLP-immunized mice from EAE in an adoptive transfer setting.

At the molecular level, cell differentiation via the AT_1 receptor involves multiple G protein-dependent and -independent signaling pathways, resulting in activation of signal transducer and activator of transcription (STAT) molecules. In a classical paradigm, STAT4 is also involved in the differentiation of T cells to "Th1" or "Th17" cells (33, 34). Consistent with these data, STAT4-deficient mice are resistant to EAE (35). Well in line with these concepts, PLP139-151-immunized SJL/J mice showed reduced levels of STAT1 and STAT4 protein levels after treatment with lisinopril and displayed a reduced responsiveness to lL-12. Moreover, treatment of antigen-specific T cells with lisinopril modulated suppressor of cytokine signaling (SOCS) molecules, which may additionally contribute to a regulatory "Th2" cell phenotype. SOCS molecules may also negatively regulate nuclear factor NF-κB, a transcription factor involved in many inflammatory responses (36). In turn, NF-κB inhibition enhances the activity of FOXP3 and thus the induction of Treg cells. Well in line with this concept, lisinopril was shown to induce the expression of the inhibitor of NF-κB, IκBα, in APCs, thus suppressing NF-κB pathways and inducing FOXP3-positive Treg.

Besides effects on T cells, recent data also suggest pivotal effects of the RAAS on CD11b-positive as well as CD11c-positive APCs. In particular, blockade of AT_{1b} receptors via losartan affects the migration of APCs, thus limiting the numbers of macrophages and DCs in the spleen under inflammatory conditions, as well as in the inflamed CNS. These findings, and in particular studies in AT_{1a} receptor-deficient mice (*agtr1*$^{-/-}$ mice), identify the AT_{1b} receptor as the pivotal mediator of the RAAS involved in the function of APCs in autoimmunity. However, migration of CD11b-positive monocytes may not only play a role in the pathogenesis of MS, but also cardiovascular diseases such as atherosclerosis, where chemokines and their receptors, such as CCL2 and CCR5, may be involved (5, 6). Indeed, inhibition of the RAAS at the level of ACE or the AT_1 receptor was shown to affect adhesion of monocytes to blood vessels or migration of monocytes into atherosclerotic plaques. Moreover, blockade of the AT_1 receptor may also inhibit the accumulation of DCs in a rat model of tubulointerstitial fibrosis. Here, Ang II may not only interfere with APC migration, but also with APC differentiation, which deserves further investigation.

In MOG-EAE, the inhibition of APC migration may be mediated by an effect of the RAAS on the expression of chemokines such as CCL2. In line with this observation, the ACE inhibitor ramipril reduced the Ang II-induced release of the chemokines IL-8 and CCL2 in monocytes via NF-κB-dependent mechanisms. A reduction of CCL2 in monocytes was also shown after losartan treatment in a rat model of spontaneous hypertension and in a model of mesangial proliferative glomerulonephritis. Besides inhibition of chemokine expression, AT_1 receptor blockade may also affect chemokine receptor expression in monocytes, as shown recently for the chemokine receptors CXCR2 and CCR2.

Besides the function of AT_1 receptors, transfer experiments with bone marrow stromal cells in a model of ischemia–reperfusion injury also pointed to a role for the AT_2 receptor in the regulation of promigratory chemokines (37). However, in cell culture experiments, AT_1 and AT_2 receptor antagonists were not able to completely suppress the immunological effects of Ang II, suggesting that complex regulatory mechanisms may play a role. In summary, the RAAS plays an important role in immune cell migration during autoimmune demyelination of the CNS. These observations in several animal models may well relate to MS, where levels of serum ACE activity were suggested as an indicator of disease activity.

Besides direct actions of the RAAS, downstream effectors may also be involved in autoimmune reactions. It has already been shown that aldosterone, a mineralocorticoid which is Ang II-dependently released from the adrenal cortex, promotes proinflammatory processes such as perivascular inflammation, reactive oxygen species production, immune complex deposition and immune cell infiltration, leading to cardiovascular and renal diseases (38-40). Classically, aldosterone contributes to the reabsorption of sodium and water in the renal tubule. Excessive production of aldosterone leads to the development of hypertension and cardiovascular disease, and it may thus already generate a proinflammatory state (41).

However, a direct effect on adaptive immune functions was only recently reported. This recent study described the modulation of DC function by aldosterone (42). In a cell culture system, ovalbumin-specific $CD8^+$ T cells were cocultured with aldosterone-pretreated,

ovalbumin-pulsed DCs. In this model, aldosterone led to an increased activation of $CD8^+$ T cells, as shown by upregulation of the activation marker CD69 and the expression of IL-2. Furthermore, aldosterone increased the secretion of IFN-γ by ovalbumin-specific T cells. The functional role of the mineralocorticoid receptor (MR) was underlined by the observation that T-cell priming was inhibited by two MR blockers: the competitive aldosterone inhibitor spironolactone and the MR antagonist eplerenone. Spironolactone alone inhibited the activation of $CD8^+$ T cells, as measured by IL-2 secretion. Additional analyses revealed that aldosterone-induced enhancement of T-cell activation is mediated through DCs and not caused by a direct effect on T-cell function. Consistently, the MR was detected in DCs but no significant MR expression was found in $CD4^+$ and $CD8^+$ T cells. Since it has been shown that DCs are required for the aldosterone-induced activation of $CD8^+$ T cells, the functional role of the MR in DCs was further studied. Treatment with aldosterone did not affect phagocytic capacity or maturation of DCs, as determined by expression of CD80, CD86 or CD40 as co-stimulatory molecules. However, aldosterone significantly decreased the expression of programmed death 1 ligand 1 (PD-L1 or B7-H1), a costimulatory ligand that suppresses $CD8^+$ T-cell activity. Furthermore, aldosterone contributed to an altered cytokine profile in DCs, with increased IL-6 and TGF-β secretion in response to aldosterone, whereas secretion of IL-10 and IL-12 was not affected. In line with this observation, spironolactone prevented the induction of IL-6 and TGF-β expression in response to aldosterone. The mechanisms involved in aldosterone-dependent modulation of DCs encompassed activation of the mitogen-activated protein kinases (MAPK), including p38 and JNK, while ERK-1 and ERK-2 were not modulated.

Finally, the question arose as to whether aldosterone-activated DCs also possess the capacity to polarize naïve $CD4^+$ T cells towards a "Th17" phenotype. Indeed, aldosterone-treated DCs displayed an enhanced capacity to promote IL-17 production in $CD4^+$ T cells. Induction of IL-17 secretion was suppressed by the aldosterone inhibitor spironolactone and the MR antagonist eplerenone. The "Th17"-inducing capacity of aldosterone was also observed in vivo: application of aldosterone worsened the course of EAE. In addition, blockade of the MR prevented all aldosterone effects on DCs and attenuated EAE in aldosterone-treated mice.

CONCLUSIONS

In summary, an increasing wealth of data point to the importance of the RAAS in neuroinflammation. Thus, modulators of the RAAS, including renin or ACE inhibitors, AT_1 receptor blockers, and possibly also MR blockers, may pose new and interesting therapeutic options in such conditions. These drugs are used by millions of people worldwide for cardiovascular indications with good tolerability; no long-term adverse effects on the immune system have been reported so far. In view of the potentially severe side effects of some innovative oral MS therapeutics currently under development, controlled studies with drugs targeting the RAAS in MS or other autoimmune diseases are highly warranted.

DISCLOSURES

Dr. Gold has received speaker's fees, consulting honoraria and grant support from Biogen, Teva, Bayer Schering, Merck Serono and Novartis. The other authors state no conflicts of interest.

REFERENCES

1. Goodfriend, T.L., Elliott, M.E., Catt, K.J. *Angiotensin receptors and their antagonists*. N Engl J Med 1996, 334(25): 1649-54.
2. Crowley, S.D., Gurley, S.B., Herrera, M.J. et al. *Angiotensin II causes hypertension and cardiac hypertrophy through its receptors in the kidney*. Proc Natl Acad Sci U S A 2006, 103(47): 17985-90.
3. Foster, R.H., MacFarlane, C.H., Bustamante, M.O. *Recent progress in understanding aldosterone secretion.* Gen Pharmacol 1997, 28(5): 647-51.
4. Benter, I.F., Yousif, M.H., Dhaunsi, G.S., Kaur, J., Chappell, M.C., Diz, D.I. *Angiotensin-(1-7) prevents activation of NADPH oxidase and renal vascular dysfunction in diabetic hypertensive rats*. Am J Nephrol 2008, 28(1): 25-33.
5. Combadiere, C., Potteaux, S., Rodero, M. et al. *Combined inhibition of CCL2, CX3CR1, and CCR5 abrogates Ly6C(hi) and Ly6C(lo) monocytosis and almost abolishes atherosclerosis in hypercholesterolemic mice*. Circulation 2008, 117(13): 1649-57.
6. Griendling, K.K., Lassegue, B., Alexander, R.W. *Angiotensin receptors and their therapeutic implications*. Annu Rev Pharmacol Toxicol 1996, 36281-306.
7. Wick, G., Knoflach, M., Xu, Q. *Autoimmune and inflammatory mechanisms in atherosclerosis*. Annu Rev Immunol 2004, 22361-403.
8. Hansson, G.K., Libby, P. *The immune response in atherosclerosis: A double-edged sword*. Nat Rev Immunol 2006, 6(7): 508-19.
9. Guzik, T.J., Hoch, N.E., Brown, K.A. et al. *Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction.* J Exp Med 2007, 204(10): 2449-60.
10. Crackower, M.A., Sarao, R., Oudit, G.Y. et al. *Angiotensin-converting enzyme 2 is an essential regulator of heart function.* Nature 2002, 417(6891): 822-8.
11. Oudit, G.Y., Kassiri, Z., Patel, M.P. et al. *Angiotensin II-mediated oxidative stress and inflammation mediate the age-dependent cardiomyopathy in ACE2 null mice*. Cardiovasc Res 2007, 75(1): 29-39.
12. Santos, R.A., Simoes e Silva, A.C., Maric, C. et al. *Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas*. Proc Natl Acad Sci U S A 2003, 100(14): 8258-63.
13. Stegbauer, J., Vonend, O., Oberhauser, V., Rump, L.C. *Effects of angiotensin-(1-7) and other bioactive components of the renin-angiotensin system on vascular resistance and noradrenaline release in rat kidney*. J Hypertens 2003, 21(7): 1391-9.
14. Stegbauer, J., Oberhauser, V., Vonend, O., Rump, L.C. *Angiotensin-(1-7) modulates vascular resistance and sympathetic neurotransmission in kidneys of spontaneously hypertensive rats*. Cardiovasc Res 2004, 61(2): 352-9.
15. Loot, A.E., Roks, A.J., Henning, R.H., Tio, R.A., Suurmeijer, A.J., Boomsma, F., van Gilst, W.H. *Angiotensin-(1-7) attenuates the development of heart failure after myocardial infarction in rats*. Circulation 2002, 105(13): 1548-50.
16. Lovren, F., Pan, Y., Quan, A. et al. *Angiotensin converting enzyme-2 confers endothelial protection and attenuates atherosclerosis.* Am J Physiol Heart Circ Physiol 2008, 295(4): H1377-H1384.
17. Muller, D.N., Shagdarsuren, E., Park, J.K. et al. *Immunosuppressive treatment protects against angiotensin II-induced renal damage.* Am J Pathol 2002, 161(5): 1679-93.
18. Dragun, D., Muller, D.N., Brasen, J.H. et al. *Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection*. N Engl J Med 2005, 352(6): 558-69.
19. Clasen, R., Schupp, M., Foryst-Ludwig, A. et al. *PPARgamma-activating angiotensin type-1 receptor blockers induce adiponectin.* Hypertension 2005, 46(1): 137-43.

20. Stadelmann, C., Albert, M., Wegner, C., Bruck, W. *Cortical pathology in multiple sclerosis.* Curr Opin Neurol 2008, 21(3): 229-34.
21. Wujek, J.R., Bjartmar, C., Richer, E., Ransohoff, R.M., Yu, M., Tuohy, V.K., Trapp, B.D. *Axon loss in the spinal cord determines permanent neurological disability in an animal model of multiple sclerosis.* J Neuropathol Exp Neurol 2002, 61(1): 23-32.
22. Gold, R., Linington, C., Lassmann, H. *Understanding pathogenesis and therapy of multiple sclerosis via animal models: 70 Years of merits and culprits in experimental autoimmune encephalomyelitis research*. Brain 2006, 129(Pt. 8): 1953-71.
23. Herrero-Herranz, E., Pardo, L.A., Gold, R., Linker, R.A. *Pattern of axonal injury in murine myelin oligodendrocyte glycoprotein induced experimental autoimmune encephalomyelitis: Implications for multiple sclerosis.* Neurobiol Dis 2008, 30(2): 162-73.
24. Stegbauer, J., Lee, D.H., Seubert, S. et al. *Role of the renin-angiotensin system in autoimmune inflammation of the central nervous system*. Proc Natl Acad Sci U S A 2009, 106(35): 14942-47.
25. Han, M.H., Hwang, S.I., Roy, D.B. et al. *Proteomic analysis of active multiple sclerosis lesions reveals therapeutic targets*. Nature 2008, 451(7182): 1076-81.
26. Platten, M., Youssef, S., Hur, E.M. et al. *Blocking angiotensin-converting enzyme induces potent regulatory T cells and modulates TH1- and TH17-mediated autoimmunity*. Proc Natl Acad Sci U S A 2009, 106(35): 14948-53.
27. Constantinescu, C.S., Ventura, E., Hilliard, B., Rostami, A. *Effects of the angiotensin converting enzyme inhibitor captopril on experimental autoimmune encephalomyelitis.* Immunopharmacol Immunotoxicol 1995, 17(3): 471-91.
28. Okunuki, Y., Usui, Y., Nagai, N., Kezuka, T., Ishida, S., Takeuchi, M., Goto, H. *Suppression of experimental autoimmune uveitis by angiotensin II type 1 receptor blocker telmisartan.* Invest Ophthalmol Vis Sci 2009, 50(5): 2255-61.
29. Zhao, X.L., Li, G.Z., Sun, B. et al. *MMP-mediated cleavage of beta-dystroglycan in myelin sheath is involved in autoimmune neuritis.* Biochem Biophys Res Commun 2010, 392(4): 551-6.
30. McMahon, E.J., Bailey, S.L., Castenada, C.V., Waldner, H., Miller, S.D. *Epitope spreading initiates in the CNS in two mouse models of multiple sclerosis.* Nat Med 2005, 11(3): 335-9.31
31. Steinman, L. *A brief history of T(H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage*. Nat Med 2007, 13(2): 139-45.
32. Komiyama, Y., Nakae, S., Matsuki, T. et al. *IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis.* J Immunol 2006, 177(1): 566-73.
33. Mathur, A.N., Chang, H.C., Zisoulis, D.G. et al. *Stat3 and Stat4 direct development of IL-17-secreting Th cells.* J Immunol 2007, 178(8): 4901-7.
34. Nishikomori, R., Usui, T., Wu, C.Y., Morinobu, A., O'Shea, J.J., Strober, W. *Activated STAT4 has an essential role in Th1 differentiation and proliferation that is independent of its role in the maintenance of IL-12R beta 2 chain expression and signaling.* J Immunol 2002, 169(8): 4388-98.
35. Chitnis, T., Najafian, N., Benou, C., Salama, A.D., Grusby, M.J., Sayegh, M.H., Khoury, S.J. *Effect of targeted disruption of STAT4 and STAT6 on the induction of experimental autoimmune encephalomyelitis*. J Clin Invest 2001, 108(5): 739-47.
36. Kinjyo, I., Hanada, T., Inagaki-Ohara, K. et al. *SOCS1/JAB is a negative regulator of LPS-induced macrophage activation.* Immunity 2002, 17(5): 583-91.
37. Iwanami, J., Mogi, M., Li, J.M. et al. *Deletion of angiotensin II type 2 receptor attenuates protective effects of bone marrow stromal cell treatment on ischemia-reperfusion brain injury in mice*. Stroke 2008, 39(9): 2554-59.
38. Brown, N.J. *Aldosterone and vascular inflammation*. Hypertension 2008, 51(2): 161-7.
39. Gurley, S.B., Allred, A., Le, T.H. et al. *Altered blood pressure responses and normal cardiac phenotype in ACE2-null mice*. J Clin Invest 2006, 116(8): 2218-25.
40. Williams, J.S., Williams, G.H. *50th anniversary of aldosterone 6*. J Clin Endocrinol Metab 2003, 88(6): 2364-72.
41. Takeda, Y. *Role of cardiovascular aldosterone in hypertension*. Curr Med Chem Cardiovasc Hematol Agents 2005, 3(3): 261-6.
42. Herrada, A.A., Contreras, F.J., Marini, N.P. et al. *Aldosterone promotes autoimmune damage by enhancing Th17-mediated immunity.* J Immunol 2010, 184(1): 191-202.