Treatment of Experimental Myocarditis via Modulation of the Renin-Angiotensin System

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Abstract: The renin-angiotensin system is primarily responsible for regulating vascular tone. Drugs that inhibit this pathway, angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists, are widely used to treat hypertension and a variety of cardiomyopathies. Recent studies have shown that, in addition to reducing blood pressure, these drugs also modulate inflammation, adhesion molecule expression, and fibrosis. To assess the therapeutic potential of these inhibitory agents for the treatment of inflammatory heart disease, the drugs have been tested in experimental models of infectious and autoimmune myocarditis. This review summarizes the results of studies examining the efficacy of angiotensin converting enzyme inhibitors and angiotensin receptor antagonists for the treatment of mouse models of virus-induced and parasite-induced myocarditis, as well as autoimmune cardiomyopathy. The collective results strongly support the use of renin-angiotensin modulation for the treatment of myocarditis. Importantly, this therapeutic approach seems to downregulate autoimmunity without causing immune suppression which may enhance the survival of the disease-initiating infectious agent.

Key Words: Angiotensin converting enzyme, angiotensin, renin-angiotensin system, immunity, myocarditis, autoimmunity, cardiac.

HEART FAILURE AND MYOCARDITIS

Heart failure can result from a variety of disease states involving many systems in which the metabolic demands of the body can no longer be met by the oxygen-delivering capacity of the cardiovascular system. Conditions that lead to cardiac failure include structural abnormalities such as shunts and outflow tract obstruction by tumors or thrombi, valve abnormalities, diseases of the large vessels such as coarctation of the aorta, restrictive diseases such as pericarditis, and inflammatory states such as infectious myocarditis, among many others. Myocarditis, inflammation of the heart, is characterized by mononuclear cell infiltration of the heart, with or without edema or fibrosis. An inflamed or fibrotic heart is a less effective pump than a normal heart and often exhibits reduced function [1, 2]. Myocarditis is a major cause of death of young children and it is estimated that 2,500 individuals develop myocarditis each year [3, 4]. Under conditions of high blood pressure, increased stroke force is required to maintain adequate cardiac output and prolonged exposure to an increased cardiac load can cause cardiac hypertrophy, decrease cardiac output, and ultimately lead to heart failure. The kallikrein-kinin system (KKS) and the renin-angiotensin system (RAS) are endocrine pathways that play a vital role in cardiac function by acting in opposition to regulate vascular pressure.

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THE KALLIKREIN-KININ SYSTEM AND THE RENIN-ANGIOTENSIN SYSTEM

The KKS is constitutively active, with roles in a variety of biological processes, but it primarily acts to promote vasodilatation [5]. In the KKS, kininogen, which is synthesized in the liver, is cleaved by plasma and tissue kallikreins into the vasoactive peptide bradykinin [5-8], which binds to the bradykinin type 2 receptor to promote vasodilatation. Angiotensin converting enzyme (ACE) is the main enzyme responsible for degradation of bradykinin [8, 9]. ACE is a bivalent dipeptidyl carboxyl metallopeptidase present in soluble form in bodily fluids and as a membrane bound form on endothelial, epithelial or neuroepithelial cells of several organs including the heart. ACE regulates the balance between the KKS and RAS by cleaving the C-terminal dipeptide Phe-Arg from bradykinin, leading to its inactivation, and by binding to angiotensin I (AngI) to cleave its C-terminal dipeptide, His-Leu, creating angiotensin II (AngII), respectively [10].

The RAS promotes vasoconstriction. In the RAS, angiotensinogen, a product of the α-globin gene, is constitutively expressed in the liver and upregulated during the acute phase of an immune response [11, 12]. Renin, a kidney-derived enzyme, cleaves angiotensinogen into AngI, which is retained in the circulation until it is again cleaved into the vasoactive octapeptide, AngII, by ACE, cathepsins, or other enzymes [1, 11, 12]. The enzymes responsible for the generation of AngII are expressed by neutrophils, monocytes, epithelial cells, endothelial cells, vascular smooth muscle cells and a variety of white blood cells [1, 11, 12]. AngII functions by binding to one of two receptors, AngII receptor...
type I (AT\(_1\)R) or AngII receptor type II (AT\(_2\)R). AT\(_1\)R is constitutively expressed in all tissues except the adrenal gland and pituitary gland. AT\(_2\)R is constitutively expressed in the adrenal gland, brain, and testis but can be upregulated in AT\(_1\)R-expressing cells upon AT\(_1\)R stimulation [1].

When activated by AngII, AT\(_1\)R is internalized and recycled, while AT\(_2\)R is retained on the cell surface [1]. Therefore, AT\(_2\)R signaling dominates when both receptors are stimulated. Stimulation of AT\(_1\)R promotes cellular proliferation, extracellular matrix production, vasoconstriction, induces the expression of P-selectin, ICAM-1, VCAM-1, IL-1\(\alpha\), IL-1\(\beta\), IL-2, IL-6, IL-12, IFN-\(\gamma\), MCP-1, TNF-\(\alpha\) and TGF-\(\beta\) and increases oxygen radical formation and activation of NFkB [1, 11, 12]. The stimulation of AT\(_2\)R antagonizes signaling through AT\(_1\)R by inhibiting cellular proliferation and promoting apoptosis, but AT\(_2\)R signaling also increases oxygen radical formation and activates NFkB in the same manner as does AT\(_1\)R. An outstanding article by Dostal and Baker reviews the evidence suggesting the presence of a functional cardiac-specific RAS [13]. In summary, any tissue insult or immune system stimulus that leads to increased production of AngII can constrict local blood vessels, increase blood pressure, and promote inflammation. Such insults occurring in heart tissue can lead to cardiac hypertrophy or myocarditis.

INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM

Drugs employed to specifically inhibit the RAS target ACE activity or prevent binding of AngII to the AngII receptor (ATR). ACE inhibitors are drugs that block the formation of AngII from AngI, and the breakdown of bradykinin by binding to ACE through its peptide-binding pocket. A large number of ACE inhibitors are commonly prescribed today, including captopril, enalaprilat, enalapril, lisinopril, quinapril, ramipril, trandolapril and zofenopril. ATR antagonists, such as losartan and PD123319, interact with the transmembrane region of the receptor and inhibit the binding of AngII. As previously discussed, AngII is a potent vasoconstrictor and immunomodulator. Therefore, ACE inhibitors and ATR antagonists are commonly prescribed both as a first course and as continued treatment for infectious and autoimmune myocarditides. While many experimental animal models have been used to explore the usefulness of modulating the RAS in heart failure and hypertension [14], less has been done to examine the efficacy of the treatments in animal models of myocarditis. It is important to understand the mechanisms by which these agents improve inflammatory conditions, especially since there may be several operating simultaneously.

MYOCARDITIS

Myocarditis can have multiple causes, including bacterial, viral or parasitic infections or exposure to cardiotoxic drugs and other agents [3, 15-17]. The infectious agents may induce myocarditis via immune molecular mimicry leading to autoimmunity, myocardic damage or death, or disruption of the cardiac extracellular matrix. The immune system helps to identify and eliminate infected cells, and participates in the repair of damaged cardiac tissue. During the repair process, immunity to self-antigens may develop in some individuals. For instance, autoantibodies specific for cardiac antigens are produced in a variety of human inflammatory heart diseases, including idiopathic dilated cardiomyopathy [16, 18-20], tuberculous pericarditis [21], Lyme carditis [22], rheumatic heart disease [23], Chagas heart disease [24] and inflammatory states of unknown etiology [25].

Cellular autoimmune responses have been similarly detected. Peripheral blood mononuclear cells from patients with rheumatic heart disease react with myocardial antigens [26], and cardiac antigen-specific T cell clones have been isolated from human hearts with rheumatic heart disease [27], and Chagas heart disease [24, 28, 29]. Cardiac myosin heavy chain is the antigen recognized in most cases of cardiac-specific autoimmunity [18, 27, 30].

TREATMENT OF MYOCARDITIS WITH ACE INHIBITORS

ACE inhibitors are widely used to treat patients suffering from a variety of cardiomyopathies including idiopathic dilated cardiomyopathy [31] and Chagas heart disease [32], among others [33]. Experimental models of myocarditis have been valuable for discovering that ACE inhibitors can prevent myocardial fibrosis in the hypertensive rat [34], or in mice with myocarditis caused by infection with coxsackievirus B3 (CB3) [35], encephalomyocarditis virus (EMCV) [36] or Trypanosoma cruzi, the parasite that causes Chagas disease [37]. The initial rationale for inhibiting ACE activity was to promote vasodilation and decrease cardiac burden. Since ACE is responsible for the production of AngII from AngI and the degradation of bradykinin into inactive peptides, ACE inhibition prevents AngII formation and blocks vasoconstriction. At the same time, these inhibitors prevent the degradation of bradykinin, which promotes vasodilation. Surprisingly, ACE inhibitors have other beneficial effects that decrease the severity of heart disease, including antifibrotic effects mediated by prevention of fibroblast proliferation and inhibition of extracellular matrix production [38]. This inhibition has the secondary benefit of improving myocyte contractility and structure [39]. Since the relative efficacies of ACE inhibition and ATR antagonism for the treatment of heart failure and hypertension have been compared [40], we will restrict our discussion to the relatively small number of studies involving animal models of myocarditis.

EXPERIMENTAL AUTOIMMUNE AND INFECTIOUS MYOCARDITIS MODELS

To determine how to eliminate infectious agents causing myocarditis and to characterize the potential significance of autoimmunity to disease pathogenesis, several cardiac antigen-induced myocarditis models were developed. Overall, cardiac myosin is the most effective myocarditis-inducing cardiac antigen [41], although only some strains of mice are susceptible to cardiac autoimmunity [41]. Experimental autoimmune myocarditis (EAM) is histologically similar to human myocarditis, with myocyte swelling and necrosis accompanied by mononuclear cell infiltration and fibrosis. CD4\(^+\) and CD8\(^+\) T cells are recruited into the heart infiltrate and contribute to the pathogenesis of EAM [41, 42]. Plasma cells can be identified in the heart but adoptive transfer of antibodies does not induce disease [43]. The pathogenesis of EAM in A/J mice exhibits a T helper type 2 (Th2) cytokine
profile [44], but confirmation of this phenotype through analysis of ex vivo cytokine production from T cells specific for cardiac antigens is lacking. Several Th1 cytokines, including IFN-γ, TNF-α and IL-12, are also notably important to the severity of EAM [45].

Viral models of disease, using cardiotropic EMCV or CB3, are the most extensively studied models of myocarditis. Both diseases have three phases including: (i) an acute phase occurring within the first few days, (ii) a sub-acute phase occurring between 4-14 days post-infection, and (iii) a chronic phase extending throughout the life of the animal. Death can occur in the acute phase due to severe viral infection in the absence of cardiac inflammation. In the subacute phase, heart failure is concurrent with inflammation, which is characterized by infiltration of natural killer cells and accumulation of fibrotic tissue. The recruitment of macrophages and lymphocytes seven days following infection ultimately contributes to the development of the most severe cardiac damage in these models of disease. Viruses cannot be cultured from heart tissue during the chronic phase despite extensive cardiac inflammation and damage. Furthermore, immunosuppressive therapy leads to increased viral titers without improving cardiac pathology [3, 41].

Infectious myocarditis can also be induced in susceptible mice with the protozoan T. cruzi [46], the causative agent of human Chagas heart disease. After infection, T. cruzi enters the bloodstream, invades cardiomyocytes, replicates in the cytoplasm, and is released upon myocyte lysis. Chagas disease has acute and chronic phases. Parasites are typically detected in the blood during the acute phase but not in the chronic phase, yet cardiomyopathy is usually seen in the chronic phase of disease resulting in death in one out of three infected individuals. The acute phase of Chagas heart disease is characterized by a focal inflammation in the myocardium composed of mononuclear cells (lymphocytes, macrophages, and plasma cells), mast cells, and granulocytes [47]. Significant parasitosis is typically observed in both cardiac and skeletal muscle. Acute myocarditis frequently resolves after a few months, after which the disease enters the chronic phase. This phase is characterized by development of a globose heart with a rounded apex due to biventricular hypertrophy and chamber dilatation. The exudate in chronic chagasic myocarditis is mainly composed of lymphocytes and, to a lesser degree, macrophages, eosinophils, plasma cells, neutrophils, and mast cells [48]. T lymphocytes predominate, with nearly three times as many CD8+ T cells than CD4+ T cells. There may also be myofibrillar destruction and replacement by connective tissue, leading to progressive fibrosis.

ACE INHIBITORS AND ATR ANTAGONISTS IN EXPERIMENTAL AUTOIMMUNE MYOCARDITIS

To assess the contribution of the RAS to EAM, our laboratory used captopril, an ACE inhibitor [49], and losartan, an ATR antagonist (Bahk et al., submitted for publication), to treat animals immunized with myosin emulsified in complete Freund’s adjuvant. The effect of treatment on EAM was assessed by measuring cardiac enlargement, inflammation, fibrosis, delayed-type hypersensitivity (DTH), and antibody production. To determine the effect of treatment on cardiac enlargement, we assessed the heart weight (HW) to body weight (BW) ratio of treated and untreated mice. A significant decrease in the HW to BW ratio was observed in both captopril and losartan-treated myosin-immunized animals as compared to untreated, myosin-immunized controls. Histopathologic analysis of tissue inflammation and fibrosis in hearts removed from myosin- and saline-immunized treated mice 21 days post-immunization showed a significant reduction in the incidence and severity of myocarditis in captopril-treated, myosin-immunized mice as compared to untreated controls (Fig. 1). Losartan also significantly reduced the incidence and severity of myocarditis in myosin-immunized mice, but to a lesser extent than that seen in the captopril treated group. Fibrosis was significantly reduced in both the captopril-treated and losartan-treated, myosin-immunized mice compared to controls.

DTH responses were analyzed to investigate the effect of drug treatment on cell-mediated immune responses. At 20 days post-immunization, DTH responses were determined in myosin-immunized or saline-immunized mice by injecting the mouse ear with antigen and assessing antigen-specific ear swelling after 24 hours. Myosin-specific DTH in captopril-treated, myosin-immunized mice was significantly decreased, while myosin DTH in losartan-treated, myosin-immunized mice was unaffected. Cardiac myosin-specific antibody production was measured using ELISA to determine the effect of treatment on EAM humoral immune responses. Myosin-specific antibody production was not significantly affected by captopril treatment, although both captopril-treated and losartan-treated, myosin-immunized animals showed reduced levels of antibodies directed to total heart proteins (ref. [49] and Bahk et al., submitted for publication). Western blot analysis of sera from treated animals shows that captopril reduces or prevents antibody reactivity against mouse cardiac proteins. This could possibly be due to reduced primary tissue damage and consequent reduction in stimulation of immune responses to non-myosin antigens (epitope spreading).

In EAM, the RAS contributes significantly to disease pathogenesis (Table 1). We have determined that ACE inhibition is more effective in preventing myocarditis than ATR antagonism, but the mechanism of inhibition remains unclear (Bahk et al., submitted for publication). The RAS contributes to cytokine, chemokine, and adhesion molecule expression, as well as the production of extracellular matrix proteins. Further experimentation is needed to determine whether one or all of these pathways are affected by RAS inhibition in EAM.

ACE INHIBITORS AND ATR ANTAGONISTS IN VIRAL MYOCARDITIS

ACE inhibitors and ATR antagonists have been extensively studied in experimental models of CB3-induced or EMCV-induced myocarditis. In CB3-induced myocarditis, captopril treatment has been tested in early (days1-6), intermediate (days 10-30), and late (days 30-60) stages of disease. Mice inoculated with CB3 at day 0 and treated with captopril on days 1-6 show no change in viral titers, but did show decreased HW to BW ratios, inflammation, and necrosis [50]. In a short term model of CB3-induced myocarditis,
mice treated with captopril at day 3 post-inoculation and sacrificed at day 9 [51] had decreased HW to BW ratios and necrosis, but no change in inflammation [51]. Treatment with captopril in the intermediate phase of CB3-induced myocarditis did not alter viral titers [50], but decreased the HW to BW ratio, myofibrillar diameter, inflammation, necrosis, and fibrosis [35, 50]. Finally, treatment with captopril in the late phase of CB3-induced myocarditis did not alter disease pathogenesis with respect to control [35]. These studies, summarized in Table 1, suggest that captopril treatment can be beneficial in decreasing cardiac damage and indicate that there is a narrow window in which captopril treatment should be initiated in CB3-induced myocarditis to achieve maximal reduction of disease severity.

In EMCV-induced myocarditis, ACE inhibition with captopril and enalapril, and AT1R antagonism with losartan and L-158809 were tested for the ability to modulate acute myocarditis [52, 53]. Treatment with these drugs was initiated 7 days post-inoculation and was terminated at day 21. Both ACE inhibitors decreased the HW to BW ratio, the myofibrillar diameter, and necrosis, while only captopril was able to decrease inflammation, left ventricular wall thickness, and cavity diameter [52, 53]. L-158809 decreased myofibrillar diameter, inflammation, and necrosis whereas losartan did not [52, 53]. Losartan did decrease the left ventricular wall thickness and cavity diameter [52, 53]. Both receptor antagonists decreased the HW to BW ratio. Captopril and losartan were administered from weeks 4 to 16 to test for their ability to modulate the late phase of EMCV infection [54]. Both drugs decreased the HW to BW ratio, myofibrillar diameter, left ventricular wall thickness, and cavity diameter, while only captopril was able to decrease fibrosis [54]. The results for ACE inhibition and AT1R antagonism in EMCV-induced myocarditis, also summarized in Table 1, show that early and late therapy may reduce disease severity. Furthermore, the variability in the effects of ACE inhibition or ATR blockade suggest that these two approaches for inhibiting RAS signaling are not entirely interchangeable. The role of ACE inhibition on the KKS and its effect on cardiac inflammation in EAM clearly has to be addressed.
ACE INHIBITORS IN CHAGAS HEART DISEASE

Captopril is the only ACE inhibitor used to date to investigate the contribution of the RAS in experimental Chagas heart disease [37]. We previously found that treatment of T. cruzi-infected mice with 5 mg/L captopril, administered in the drinking water for the duration of disease did not affect the HW to BW ratio and displayed no apparent affect on the incidence of myocarditis. Analysis of humoral immunity showed that captopril does not change myosin-specific total serum IgG or IgM, and has no impact on isotype switching. Neither parasitemia nor cardiac parasitosis was changed with treatment though treatment managed to lessen the severity of cardiac-specific fibrosis and necrosis. As for cell-mediated immunity, DTH responses measured against T. cruzi lysate and cardiac myosin did show significant decreases in measurable responses in treated animals. The observed improvement in mortality in infected, treated animals previously observed [37] could be attributed to this clear reduction in cellular immunity.

To test the possibility that a higher dose of captopril may improve disease pathogenesis in acute Chagas heart disease, the concentration of captopril in the drinking water was increased to 75 mg/L [37]. The higher concentration of captopril decreased cardiac inflammation, fibrosis, and necrosis in infected animals, yet increased mortality. The cause of the increased mortality was not determined, but was not related to increased parasitemia or cardiac parasitosis since these levels were unaltered in the presence of the highest dosage.

Table 1. Summary of the Effects of RAS Modulators on Experimental Myocarditis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Inoculation and Treatment Protocols</th>
<th>Viral Titer or Parasitemia</th>
<th>Heart Wt or Heart Wt:Body Wt Ratio</th>
<th>LV Wall Thickness and Cavity Diameter</th>
<th>Myofibrillar Diameter</th>
<th>Inflammation</th>
<th>Necrosis</th>
<th>Fibrosis</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myosin in CFA</td>
<td>Captopril treatment from day of immunization</td>
<td>na</td>
<td>↓</td>
<td>nd</td>
<td>nd</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>[49]</td>
</tr>
<tr>
<td>Myosin in CFA</td>
<td>Losartan treatment from day of immunization</td>
<td>na</td>
<td>↓</td>
<td>nd</td>
<td>nd</td>
<td>↓</td>
<td>nd</td>
<td>[50] Bahk et al., submitted for publication</td>
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</tr>
<tr>
<td>CB3</td>
<td>Captopril treatment 1-6 days post inoculation</td>
<td>nc</td>
<td>↓</td>
<td>nd</td>
<td>nd</td>
<td>↓</td>
<td>↓</td>
<td>nd</td>
<td>[51]</td>
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<tr>
<td>CB3</td>
<td>Captopril treatment 3 days post inoculation</td>
<td>nd</td>
<td>↓</td>
<td>nd</td>
<td>nd</td>
<td>nc</td>
<td>↓</td>
<td>nd</td>
<td>[50]</td>
</tr>
<tr>
<td>CB3</td>
<td>Captopril treatment starting 10 days post inoculation</td>
<td>nc</td>
<td>↓</td>
<td>nd</td>
<td>nd</td>
<td>nc</td>
<td>nc</td>
<td>nd</td>
<td>[50]</td>
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<tr>
<td>CB3</td>
<td>Captopril treatment 10-30 days post inoculation</td>
<td>nd</td>
<td>↓</td>
<td>nc</td>
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<td>↓</td>
<td>[35]</td>
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<tr>
<td>CB3</td>
<td>Captopril treatment 30-60 days post inoculation</td>
<td>nd</td>
<td>nc</td>
<td>nc</td>
<td>nc</td>
<td>nc</td>
<td>nc</td>
<td>nc</td>
<td>[35]</td>
</tr>
<tr>
<td>CB3</td>
<td>Captopril treatment 7-21 days post inoculation</td>
<td>nd</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>nd</td>
<td>[52, 53]</td>
</tr>
<tr>
<td>CB3</td>
<td>Enalapril treatment 7-21 days post inoculation</td>
<td>nd</td>
<td>↓</td>
<td>nc</td>
<td>↓</td>
<td>nc</td>
<td>↓</td>
<td>nd</td>
<td>[52, 53]</td>
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<tr>
<td>CB3</td>
<td>L-158,809 treatment 7-21 days post inoculation</td>
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<td>nd</td>
<td>[53]</td>
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<tr>
<td>CB3</td>
<td>Losartan treatment 7-21 days post inoculation</td>
<td>nd</td>
<td>↓</td>
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<td>nc</td>
<td>nc</td>
<td>nd</td>
<td>[52]</td>
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<tr>
<td>CB3</td>
<td>Captopril treatment from 4-16 weeks post inoculation</td>
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<td>nd</td>
<td>nd</td>
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<td>[54]</td>
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<tr>
<td>CB3</td>
<td>Losartan treatment from 4-16 weeks post inoculation</td>
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<td>nd</td>
<td>nd</td>
<td>nc</td>
<td>[54]</td>
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<tr>
<td>T. cruzi</td>
<td>Captopril treatment from day of inoculation</td>
<td>nc</td>
<td>nc</td>
<td>nd</td>
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<td>↓</td>
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<td>[37, 55]</td>
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na, not applicable; nc, no change from controls; nd, not determined; ↓ reduction compared to controls; sp, submitted for publication.
Drug toxicity was ruled out because captopril-treated uninfected mice do not display increased mortality. Overall, these results (Table 1) show that captopril treatment decreases Chagas disease pathogenesis by decreasing inflammation, fibrosis, and necrosis in infected animals. Interestingly, treatment may decrease or enhance mortality rates in infected mice depending on the dose of drug used [37]. Further experiments are needed to determine the mechanism by which captopril treatment affects mortality.

CONCLUSIONS

The RAS was initially thought to function as an endocrine pathway that modulates the peripheral vasculature through the vasoconstrictive actions of AngII and its binding to the AT1R. Drugs that inhibit ACE, the primary enzyme responsible for AngII generation, or that block interactions between AngII and its receptor, are potent vasodilators and have secondary benefits of improving cardiac function by decreasing inflammation and fibrosis. In vivo and in vitro drug treatment shows that inhibitors of RAS signaling can modulate cellular proliferation, cytokine production, and adhesion molecule expression. To assess the therapeutic potential of this line of drug treatment to human myocarditis, treatments were tested in both infectious and purely autoimmune animal models of myocarditis. Initial concerns about the effect of the RAS on immune responses involved the possibility that inhibition of this pathway would lead to downregulation of pathogen-specific immune responses, allow unchecked replication of an infectious agent, and result in increased cellular damage. However, this notion was adequately addressed by studies showing that inhibition of the RAS decreases inflammation without enhancement of parasite and virus replication.

There is a wide range of variability in the efficacy of various ACE inhibitors and ATR antagonists in experimental models of myocarditis. These differences could be attributed to specific pharmacokinetic properties of the individual agents or the fact that some of the agents may have activities other than ACE inhibition or ATR antagonism. The answers to these questions are not fully clear and further experimentation is needed to provide a more thorough understanding of the mechanistic action of such important and widely-used therapeutics.

ABBREVIATIONS

ACE = Angiotensin converting enzyme
AngI = Angiotensin I
AngII = Angiotensin II
ATR = Angiotensin II receptor
AT\(_2\)R = Angiotensin II receptor type 1
AT\(_3\)R = Angiotensin II receptor type 2
BW = Body weight
CHD = Chagas heart disease
CB3 = Coxsackievirus B3
DTH = Delayed-type hypersensitivity
EAM = Experimental autoimmune myocarditis
EMCV = Encephalomyocarditis virus
HW = Heart weight

REFERENCES

References 56-58 are related articles recently published in Current Pharmaceutical Design.


