Connecting chronic and recurrent stress to vascular dysfunction: no relaxed role for the renin-angiotensin system

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Submitted 12 April 2010; accepted in final form 21 October 2010

The renin-angiotensin system (RAS) acts to preserve extracellular fluid (ECF) volume and blood pressure by stimulation of vasoconstriction, tubular sodium, and water reabsorption directly and via aldosterone and ADH (51). A local tissue RAS exists independently of the circulating RAS and possesses all RAS components (103). A local RAS has not only been described in a variety of solid tissues (e.g., heart, kidney) but also in a variety of circulating cells (103). The AGTR1 ANG II receptor mediates most of the known functions of ANG II (148), is widely expressed (8), and is likely to mediate the hypertensive, proinflammatory, and pro-oxidative actions of ANG II (27, 131). Specifically, AGTR1 expression in immune cells has garnered much attention in recent years because of the evident involvement of the RAS in vascular inflammation and the atherosclerotic process (16, 27, 131). Much is still unknown about the function of the RAS in different leukocyte subsets. Furthermore, the activity of the RAS with respect to immune function has largely been investigated with respect to the pathophysiology of inflammation. RAS activity is enhanced during the stress response, supposedly to maintain hemodynamic homeostasis.

is threatened by a large variety of stressors (hemorrhage, infection/sepsis, injury, etc.), the RAS could also be a central player in other pathways in the stress response, such as immune function. This review explores the supposition that the RAS is critically involved in modulating stress-induced alterations in immune function during the stress response and that prolonged or recurrent activation of the RAS by chronic or recurrent stress could lead to vascular inflammation and atherosclerosis.

ANG II is a Proinflammatory, Proatherosclerotic Molecule

Knockout of the AGT1Ra gene in hyperlipidemic apolipoprotein E (apo E)-deficient mice inhibits the formation (144) and progression (46) of atherosclerotic plaques. In chimeric apo E-deficient mice lacking AGT1Ra in cells of the bone marrow (50), aortic atherosclerotic lesions are significantly decreased after infusion with ANG II compared with chimeric mice with AGT1Ra expressed in the bone marrow (50). Plaques are more stable in bone marrow AGT1Ra-deficient mice and fewer macrophages are present within the plaques (50). This supports the idea that bone marrow-derived cells, likely macrophages, are involved in atherosclerosis via the AGTR1.

Atherogenesis requires leukocyte trafficking, margination, and transmigration (or diapedesis). ANG II via AGTR1 activation can increase leukocyte rolling (7, 106), adhesion (7,
transmigration across vessel walls, and infiltration of tissues (7, 86, 87, 92, 106, 153). Conversely, treatment of rats with AGTR1 antagonists (24, 33, 94, 113, 152, 154) and AGTR1 knockout (105, 133) decreases leukocyte infiltration. Specifically, ANG II has been shown to enhance the margination of monocytes/macrophages (33, 86, 87, 92, 94, 133, 153, 154), neutrophils (58, 87, 95, 133), and T cells. ANG II also acts on endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) to enhance the expression of chemokines, adhesion molecules such as VCAM-1 and ICAM-1 (92, 131, 135, 153), and cytokines (mediated by NF-κB and AP-1) (24, 62, 81, 107, 118, 119, 131), and to increase vascular permeability (Fig. 1). ANG II via AGTR1 can directly stimulate ECs to increase expression and release of various chemokines including MCP-1, MIP-1α, IL-8, IP-1, KC, and RANTES (131). In summary, the AGTR1 seems also a key mediator in many pathways involved in the atherosclerotic process, and many of these are mediated via circulating cells.

**ANG II Affects Cells Involved in the Immune Response**

**AGTR1 expression in immunocompetent cells.** Shimada and Yazaki (127) were the first to identify binding sites for ANG II in human mononuclear cells by autoradiography. AGTR1 gene expression has been identified in a wide range of leukocyte subsets since: in monocytes/macrophages (57, 99, 101, 111, 130, 134), granulocytes (85, 111), neutrophils (65), T lymphocytes (99, 111, 115), and B lymphocytes (99, 111, 115). Total cellular AGTR1 protein (isolated from whole cell lysates) has been identified in monocytes/macrophages (1, 69, 126), T lymphocytes (69), and natural killer (NK) cells (69). Cell surface expression of the AGTR1 has been shown in monocytes/macrophages (65, 96, 111, 126), granulocytes (85, 111), neutrophils (65), T lymphocytes (111), and B lymphocytes (111). Data are summarized in Table 1. In particular, monocytes appear to strongly express the AGTR1 and are major players in atherogenesis. How AGTR1 expression is regulated in these cell types has not been studied.

**Lymphocytes.** Crowley et al. (32) demonstrated that in vitro exposure of freshly isolated mouse splenic T cells to ANG II resulted in cytoskeletal formation and rearrangements of F-actin, which could be inhibited with AGTR1 antagonism. Such cytoskeletal rearrangements are thought to be one of the hallmarks of formation of synapses between T cells and antigen-presenting cells (32). AGTR1 antagonists can also sup-

**Table 1. Summary of data on AGTR1 gene and protein expression in immunocompetent cells**

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>mRNA (RT-PCR or qPCR)</th>
<th>Total Cellular or Cytosolic Protein (Western Blotting)</th>
<th>Surface Protein (Flow Cytometry or Immunohistochemistry)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monocytes/macrophages</td>
<td>Human primary (57, 111, 130)</td>
<td>Human primary (1, 69)</td>
<td>Human primary (96, 111)</td>
</tr>
<tr>
<td></td>
<td>Mouse primary (99)</td>
<td>Human cell line THP-1 (126)</td>
<td>Human cell line THP-1 (126)</td>
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<tr>
<td></td>
<td>Human cell line THP-1 (87, 134)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T lymphocytes</td>
<td>Human primary (111, 115)</td>
<td>Human primary (69)</td>
<td>Human primary (111)</td>
</tr>
<tr>
<td></td>
<td>Mouse primary (99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B lymphocytes</td>
<td>Human primary (111, 115)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Mouse primary (99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocytes</td>
<td>Human primary (85, 111)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Rat primary (65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NK cells</td>
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</tr>
</tbody>
</table>

AGTR1, ANG II type 1 receptor; NK, natural killer; THP, Tamm-Horsfall protein. Reference numbers are in parentheses.
press T cell production of IFN-γ (26, 121) and TNF-α (26) in vitro. ANG II has also been shown to augment lymphocyte chemotaxis. Guzik et al. (56) showed that T cell expression of CC chemokine receptor 5, which activates upon binding of certain cytokines such as RANTES and MIP-1α/β, was increased after mice were injected with ANG II. Several studies have suggested that ANG II-mediated AGTR1 activation can lead to T cell proliferation (69, 99, 139); however, this remains to be further substantiated.

ANG II may function to enhance the sensitivity of lymphocytes to infectious antigens and/or certain cytokines such that lymphocyte activation and memory cell expansion occur more rapidly during the stress response. No studies have examined the effects of ANG II on B cell function and immunoglobulin production; however, the presence of angiotensin receptors, AGTR1 specifically, does point toward some role for ANG II in modulating B cell function. It is likely that ANG II activates B cells in a way that is similar to its activating effects on T lymphocytes, and it has been shown that stress enhances both the cellular and humoral immune response to various immunological challenges. Increases in circulating ANG II during the stress response may well directly activate NK cells and B and T lymphocytes and/or augment the activation of T and B lymphocytes in response to other immune-enhancing signals, in effect increasing the sensitivity and preparedness of the adaptive immune response to imminent immune challenges.

Granulocytes. ANG II can stimulate NADPH-oxidase-dependent (59) reactive oxygen species (ROS) production in neutrophils (102, 108) via p38 MAP kinase, ERK (59, 108), and cytosolic phospholipase A2 (59). Dandona et al. (34) showed that ROS generation by neutrophils isolated from human subjects decreased significantly after subjects were treated with the AGTR1 antagonist valsartan. ANG II can inhibit the synthesis of heme oxygenase-1 in human neutrophils (5), which would diminish antioxidant capacity. In turn, ROS activates NF-κB. More directly, ANG II can increase cytosolic calcium, synthesis and activity of calcineurin, and NF-κB binding activity as shown in cultured human neutrophils (108). Dandona et al. (34) demonstrated that NF-κB DNA binding activity in the neutrophils from AGTR1 antagonist-treated subjects decreased and that expression of the protein IκB, which binds and inhibits nuclear translocation of NF-κB, increased. Whether the sequence of events from increased ANG II levels to ROS production to inflammation occurs in pathophysiological conditions is not resolved.

ANG II stimulation of granulocytes appears to be chemotactic and chemokinetic. In vitro, 10^{-10} M ANG II stimulated migration of neutrophils, whereas it fell sharply with higher concentrations. The same authors (44) reported that ANG II concentrations >10^{-10} M inhibited migration of neutrophils in response to IL-8, suggesting that ANG II has a mediating role in the control of cytokine-stimulated neutrophil chemotaxis. ANG II may also stimulate granulocyte adhesion to the vessel wall, as treatment of neutrophils isolated from the blood of patients after an ischemic stroke with candesartan, an AGTR1-specific antagonist, inhibited adhesion to cultured vascular ECs (58). It is unknown whether ANG II stimulates granulocyte phagocytosis. Altogether, increased circulating ANG II during the stress response may enhance the activity of granulocytes in such a way that responsiveness to chemotactic signals is increased and trafficking to sites of injury or infection is more rapid.

Monocytes. ANG II stimulates monocytes in vitro to increase the expression of various cytokines and inflammatory mediators, including of TNF-α (48, 57, 87), IL-8 (126), MCP-1 (126), MCP-2 (134), and tissue factor (60, 98). ANG II also stimulates monocytes to produce nitric oxide (NO) (125) and ROS (150). Furthermore, ANG II can enhance the phagocytic activity of macrophages (88, 89, 115). In vitro studies have shown that direct stimulation of monocytes with ANG II increases their adhesion to endothelial cell monolayers (1, 43, 57, 70, 132). AbdAlla et al. (1) showed that monocytes with increased levels of AGTR1 homodimers (crosslinked by the action of factor XIIIa) showed elevated levels of ANG II-stimulated adhesion, above that seen in monocytes with fewer or no AGTR1 homodimers. Unfortunately, this observation has not been reproduced. ANG II induces monocyte adhesion to vessel wall endothelium by enhancing expression of integrins, subsequently enhancing the transmigration and redistribution of monocytes to various tissues. Increased circulating ANG II during the stress response may therefore be at least partly responsible for mediating the stress-induced activation and redistribution of monocytes.

ANG II can activate monocytes via a variety of signaling pathways. AGTR1 activation by ANG II activates NF-κB (34, 60, 76, 126) and decreases the inhibitory protein IκB (34, 60). PKC, protein tyrosine kinase (PTK), and MAPK pathways can activate NF-κB in monocytes (Fig. 2). Specifically, Src kinase (a PTK), ERK 1/2, and p38 MAPK pathways are involved in ANG II/AGTR1-stimulated monocyte migration (71), which may be the result of increased NF-κB activity. Additionally, ANG II via AGTR1 can activate the JAK/STAT pathway, which is also involved in many of the proinflammatory and proliferative effects of ANG II (63). ANG II also affects NO/ROS balance in monocytes by induction of inducible nitric oxide synthase (iNOS) (125) and by induction of NADPH-oxidase (45, 150). Figure 2 illustrates potential signaling pathways that enhance the expression of proinflammatory genes following AGTR1 activation of monocytes.

Finally, AGTR1 activation in monocytes may mediate other important, nontranscriptional changes in cell function, related to cell movement and migration. Proline-rich tyrosine kinase II (Pyk2), a member of the p125 focal adhesion kinase (FAK) family, and paxillin, a focal adhesion protein, are directly associated with the cytoskeleton and are involved in cell movement and attachment (136, 155). Both Pyk2 and paxillin are highly expressed in monocytes and are phosphorylated by c-Src following stimulation of monocytes with ANG II (71, 79, 145). Upon phosphorylation, it is thought that Pyk2 translocates to focal adhesions, where it colocalizes with paxillin, resulting in cytoskeletal rearrangements and cell movement (71, 80).

Increased Systemic RAS Activity During the Stress Response is Partly Mediated by the Sympathetic Nervous System

Stress is described as a physiological and/or psychological response to a potentially harmful stimulus. The initial observations that showed increased plasma renin activity (PRA) and increased levels of circulating ANG II in animals and humans exposed to various stressors the systemic RAS date back to the
1970s. A series of small studies in healthy human male subjects demonstrated that PRA and plasma ANG II increased 30 min after an intense running exercise (74), immediately after 20 min in an 85–90°C sauna (75), and 15 min after subjects performed mental arithmetic exercises for 20 min (73). PRA increased significantly in rats exposed to a novel environment as well as in caged rats exposed to the presence of a hungry cat (29). In a more recent study using baboons, PRA increased significantly on the day that Sidman avoidance tests were administered (baboons were trained to press a lever in response to a light signal to avoid an electric shock; if the lever was not pressed, a shock was delivered), at 1, 2, and 3 h after the onset of the avoidance test (even before any shocks were delivered), and 30 min after termination (14). Increased renal renin levels, PRA, and plasma ANG II concentration upon stress are attenuated with prior \textit{H9252}\textsubscript{-}-adrenergic blockade (2, 52). Sympathetic nervous system (SNS) activation during the stress response is also responsible for increased release of catecholamines from the adrenal medulla. Similarly, it appears that activation of the efferent sympathetic renal nerves that innervate the renin-secreting granular juxtaglomerular cells is largely responsible for increasing plasma renin during the stress response.

**RAS Activation by Different Types of Stressors**

Both psychosocial/psychological stressors (mental arithmetic anxiety, threatening presence, novel environments, etc.) and physical/biogenic stressors (extremes of temperature, pain, physical exertion, etc.) increase circulating levels of ANG II (2, 21). As mentioned above, increases in PRA and/or plasma ANG II occur after exposure to psychosocial stressors in rats (29). Similarly, PRA, plasma renin concentrations, and/or plasma ANG II concentrations increased in humans in response to exercise (54, 74) and hot temperatures (85–90°C) (75). Importantly, these changes in PRA and plasma ANG II concentrations are often reported to occur despite sodium loading (2, 29, 42), indicating that increases in PRA are not a result of renal salt or water loss. Therefore, stress response pathways that bypass cognitive appraisal and pathways that begin with cognitive appraisal (stressful stimuli that have no physical component) both have the capacity to increase circulating RAS activity.

**RAS Activation in Acute vs. Chronic Stress**

Most of the above-mentioned studies have used single, time-limited acute stress protocols. Few studies have looked at the effects of persistent or intermittent chronic stressors on circulating RAS activity. Aguilera et al. (3) demonstrated that chronic intermittent stress in the form of 2 h of immobilization/day for 14 days significantly increases PRA and plasma aldosterone concentration and renin mRNA content in the kidneys 24 h after the last exposure to stress. In this same study, acute stress in the form of 30 min of immobilization resulted in significantly increased PRA and plasma aldosterone. PRA levels in this study suggest that PRA is more responsive to acute stress than to chronic stress.

Two in vivo studies have tried to directly compare the effects of acute stressors to chronic stressors on circulating RAS activity. Rats exposed to compulsive cold-water swimming for 20 min (acute stress) or to an ambient temperature of 4–8°C for 5 days (chronic stress) indicated that the acute stress enhanced plasma ANG II levels more than chronic stress (151). Cassis et al. (22) exposed rats to cold temperatures (4°C) for 7 days and assessed plasma ANG II concentrations after 4 h (acute stress), 1, 3, and 7 days. Plasma ANG II concentrations

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**Fig. 2. Potential proinflammatory AGTR1 signaling transduction pathways in monocytes.**
followed a biphasic pattern, first increasing 10-fold (after 4 h), returning to control levels after 1 and 3 days, and increasing 2-fold at 7 days of cold exposure. The increase at 7 days coincided with increase food intake.

It is known that animals exposed to the same stressful stimulus each day for several weeks show increased synthesis and storage of catecholamines in the adrenal medulla, increased basal levels of circulating catecholamines, and decreased release of catecholamines into the circulation following exposure of an identical stressor (91). However, these same chronically stressed animals show an exaggerated sympathetically-adrenal medullary response when exposed to a novel stressor, suggesting that a habituation to the chronic stressor resulted in a sensitization of the sympathetic-adrenal medullary stress response. A similar pattern of neuroendocrine adaptation may take place with the RAS but has not been documented.

**Immune Response to Stress**

**Immune cell number, trafficking, and distribution are altered by stress.** Circulating leukocyte numbers rise initially during acute stress (18, 61, 93, 97, 124), in particular granulocytes and NK cells (10, 18, 93, 97, 124). Circulating lymphocyte and monocyte numbers decrease (38, 39, 124). As the stress response continues, circulating neutrophil numbers continue to rise (38), while there is a disproportionate decrease in the absolute number of helper T cells, cytolytic T cells, B cells, NK cells, and monocytes, causing the total number of circulating leukocytes to fall below baseline (6, 124).

**Immune cell function is altered by stress.** Acute stress enhances the acquired immune response by increasing both cellular immunity (12, 40, 122, 142), and humoral immunity, particularly antibody production (31, 104, 147). Acute stress also enhances the innate immune response by increasing spleen macrophage phagocytic function (83), blood polymorphonuclear leukocyte phagocytosis (128), NK cell activity (100), as well as by increasing the proliferation of blood and spleen leukocytes (67, 82, 114, 128). Chronic stress, on the other hand, has well-documented immune-suppressing effects, and a variety of chronic stressors can suppress the skin cell-mediated immune response (9, 36), antibody production (49), NK cell activity (25, 64), leukocyte proliferation (25, 112), virus-specific T cell and NK cell activity (15), and macrophage activity (19).

**Role of endocrine factors in stress-induced immune alterations.** Despite the large focus on glucocorticoids in modulating the immune response, their role remains controversial. Endogenous glucocorticoids at pharmacological concentrations and synthetic glucocorticoids have well-described immune-suppressing effects (20). However, physiological concentrations of endogenous glucocorticoids can exert immunomodulatory, immune-enhancing, or immunosuppressive effects (35). In vitro studies indicate that both NF-κB (90) and AP-1 activity can be inhibited by glucocorticoids. However, low doses of glucocorticoids administered in vivo can enhance humoral immunity and T cell activation (4, 35, 37), suggesting that low concentrations of endogenous glucocorticoids are permissive of immune enhancement, while higher concentrations may inhibit the immune system. Catecholamines also affect immune cell activity. Adrenergic receptors are found on lymphocytes and macrophages (84), and noradrenergic sympathetic nerve fibers run from the central nervous system to both primary and secondary lymph organs (47), where noradrenalin-releasing sympathetic nerve terminals synapse with neighboring immune cells (123). Moreover, norepinephrine and small doses of epinephrine can activate cellular NF-κB in monocytes in a time- and dose-dependent manner (11). Adrenalectomy in rats eliminates stress-induced enhancement of skin cell-mediated immune responses (37). Enhancement of skin cell-mediated immunity is reduced by administration of low-dose corticosterone or epinephrine; however, simultaneous administration of both hormones produces an additive increase in the cell-mediated immune response. As such, catecholamines may be partly responsible for the immune enhancement that occurs during acute stress, while basal glucocorticoids permit immune enhancement to take place and stimulated levels of glucocorticoids prevent immune overactivity and adverse outcomes such as autoimmune-mediated tissue damage.

**ANG II Partly Mediates the Acute Enhancement of Immune Function During the Stress Response**

Despite all the information available about components of the RAS being present in immune-competent cells, the relationship between increased circulating ANG II during the stress response and stress-induced alterations in immune cell trafficking and function has not been thoroughly examined. To support a role for ANG II in modulating the immune response to stress, it must be shown that 1) stress causes enhanced leukocyte trafficking and function, 2) ANG II causes enhanced leukocyte trafficking and function, and 3) blockade of ANG II activity prevents enhanced leukocyte trafficking and function caused by stress. Only one study so far has provided a strong suggestion that activation of AGTR1 is necessary for immune alterations during stress.

Bergonzio et al. (17) showed that administration of cold-restraint stress (restraint at 4°C for 2 h) to spontaneously hypertensive rats (SHR) reduced gastric blood flow and produced acute gastric mucosal lesions. This was associated with increased expression of ICAM-1 in gastric arterial endothelium, neutrophil production of TNF-α, and neutrophil infiltration of the gastric mucosa. These effects were diminished when SHR were pretreated with the AGTR1 antagonist candesartan for 14 days before the administration of the stress protocol. Candesartan treatment increased gastric blood flow in unstressed animals; however, measurements of blood flow were lacking during cold-restraint stress. Indeed, changes in gastric and systemic hemodynamic parameters may well have affected neutrophil infiltration and the formation of gastric ulcers. However, the evidence indicating that ANG II directly alters the trafficking and function of immune cells in the in vitro studies described in the previous sections lends support to the hypothesis that activation of AGTR1 (by increased circulating ANG II) during cold-restraint stress, is at least partly responsible for enhancing the observed gastric neutrophil infiltration by direct action on neutrophil and EC AGTR1.

We therefore hypothesize that increased circulating ANG II and AGTR1 activation on leukocytes, ECs, VSMCs, among other cell types during the stress response is critically involved in the immune alterations that are observed during the acute stress response. Figure 3 provides an illustration of the potential pathways that mediate stress-induced immune alterations.
As mentioned, the evidence is limited supporting that RAS activity remains elevated in recurrent stress models (3) and in chronic stress (22, 151). We are not informed about studies regarding the possibility that recurrent and chronic stress may also increase sensitivity of the RAS to other novel stressors (91). It is likely, given the available literature that supports that ANG II is proatherogenic, that such recurrent activation, chronic activation, or sensitized overactivation of the RAS in recurrent or chronic stress situations may also lead to vascular injury and to atherogenesis.

Four mechanisms could underlie RAS-mediated atherogenesis in recurrent/chronic stress:

1) Recurrently or chronically active RAS results in recurrent or chronic activation of immune, endothelial, and vascular smooth muscle cells directly (28), which would predispose the vasculature to inappropriate inflammation.

2) Recurrent or chronic activation of RAS could positively feed back to other components of the stress response that affect cardiovascular function, including the HPA axis and glucocorticoid release (120, 137, 138), sympathetically stimulated release of catecholamines from the adrenal medulla (138), and sympathetic activity by facilitating norepinephrine release from sympathetic nerve endings and inhibiting reuptake (53). Conversely, chronic stress may lead to macula densa release of renin via the SNS.

3) Recurrent/chronic activation of RAS may induce recurrent or chronic increases in blood pressure or blood pressure fluctuations (66, 116) that may promote atherosclerosis (109).

4) Finally, recurrent/chronic activation of RAS may increase the sensitivity of RAS and other physiological stress response systems to other, novel stressors as occurs with the adrenal medullary response (catecholamine release) (91), which would perpetuate the proinflammatory and atherogenic actions of the RAS response. Acting together, these four RAS-mediated effects likely contribute to the development of atherosclerosis in individuals experiencing recurrent or sustained chronic stress.

**Conclusions and Perspectives**

In this review, we propose that the RAS is intimately involved with the stress response and ANG II is a major stress hormone, like the glucocorticoids and catecholamines. Circulating immune cells are expressing the AGTR1 and seem to be responsive to the actions of ANG II. RAS activity and circulating levels of ANG II increase in response to acute stressors as a result of sympathetic stimulation of juxtaglomerular cells. Recurrent stressors or chronic sustained stressors may also result in elevated levels of RAS activity and ANG II levels but may also increase the responsiveness of the RAS to novel stressors. ANG II likely has a physiological purpose in the stress response by acutely maintaining extracellular fluid volume and blood pressure and by enhancing immune function.

ANG II is now recognized to have potent proinflammatory effects and cells of the vascular wall, including ECs and VSMC, as well as the spectrum of leukocytes, express ANG II receptors. The actions of ANG II on immune and vascular cells stimulate chemotaxis, margination, and diapedesis and hence redistribution as well as a direct enhancement of immune cell function, including phagocytosis and cytokine production. It is the view of the authors that increased RAS activity and increased circulating levels of ANG II, among other factors,
are directly involved in mediating acute stress-induced immune enhancement. Such an enhancement primes the immune system to respond to immune challenges that may result from an encounter with a potentially harmful stimulus.

We would like to underscore one important consideration regarding the divergence between physiological and pathophysiological adaptations of what we would call the “cellular circulating RAS.” Many studies now indicate a clear divergence in disease states between circulating plasma components of the RAS with tissue (vascular, kidney) RAS (140, 141, 149). Information about the cellular circulating RAS is limited. In fact, the effects of a low-sodium diet on monocyte and other circulating cells AGTR1 expression and function have never been studied. Therefore, our hypothesis that chronic stress also leads to activation of the cellular circulating RAS includes that it is accompanied by inappropriate expression of AGTR1 and perhaps other components of the RAS in circulating cells.

There appears to be a link between chronic stress and the development of atherosclerosis; however, the precise mechanisms behind this link are currently not well defined. While the role of the RAS during recurrent or chronic sustained stress is incompletely understood, available evidence suggests that RAS activity may be sustained or sensitized to novel stressors in response to recurrent or chronic stressors. Inappropriately sustained or hyperreactive RAS activity, including inappropriately expressed AGTR1, in recurrent or chronic stress may be involved in the development and acceleration of atherosclerosis through hemodynamic and proinflammatory effects and through effects on other pathways of the stress response. The pleiotropic beneficial actions of inhibition of the RAS to prevent atherosclerosis may be partly mediated by the interruption of the pathways linking the stress response to immune cells and inflammation via the RAS.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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