Mechanisms of Sympathetic Regulation in Cardiovascular Disease

The brain renin-angiotensin system and cardiovascular responses to stress: insights from transgenic rats with low brain angiotensinogen

Amy C. Arnold, Atsushi Sakima, Sherry O. Kasper, Sherry Vinsant, Maria Antonia Garcia-Espinosa, and Debra I. Diz

The Hypertension & Vascular Research Center and the Departments of General Surgery and Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, North Carolina

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Arnold AC, Sakima A, Kasper SO, Vinsant S, Garcia-Espinosa MA, Diz DI. The brain renin-angiotensin system and cardiovascular responses to stress: insights from transgenic rats with low brain angiotensinogen. J Appl Physiol 113: 1929–1936, 2012. First published September 13, 2012; doi:10.1152/japplphysiol.00569.2012.—The renin-angiotensin system (RAS) has been identified as an attractive target for the treatment of stress-induced cardiovascular disorders. The effects of angiotensin (ANG) peptides during stress responses likely result from an integration of actions by circulating peptides and brain peptides derived from neuronal and glial sources. The present review focuses on the contribution of endogenous brain ANG peptides to pathways involved in cardiovascular responses to stressors. During a variety of forms of stress, neuronal pathways in forebrain areas containing ANG II or ANG-(1–7) are activated to stimulate descending angiotensinergic pathways that increase sympathetic outflow to increase blood pressure. We provide evidence that glia-derived ANG peptides influence brain AT1 receptors. This appears to result in modulation of the responsiveness of the neuronal pathways activated during stressors that elevate circulating ANG peptides to activate brain pathways involving descending hypothalamic projections. It is well established that increased cardiovascular reactivity to stress is a significant predictor of hypertension and other cardiovascular diseases. This review highlights the importance of understanding the impact of RAS components from the circulation, neurons, and glia on the integration of cardiovascular responses to stressors.

THE RENIN-ANGIOTENSIN SYSTEM (RAS) plays a critical role in the regulation of cardiovascular function and development of cardiovascular-related diseases. Independent from the circulating system, angiotensin (ANG) II produced locally within the brain has been implicated in cardiovascular regulation through AT1 receptors localized to brain regions integral to autonomic control (4, 52, 62). The brain RAS also participates in a variety of other physiological functions including modulation of cardiovascular responses to stressors (whether behavioral, surgical/anesthesia, dehydration, excess or deficits in dietary sodium, hemorrhage, etc.) through receptors localized to the hypothalamic-pituitary-adrenal (HPA) axis (1, 29, 31, 50, 64, 65, 83). ANG II enhances pressor responses to stress arising from diverse stimuli, and many of these effects are prevented by chronic administration of AT1 receptor blockers (ARBs). These observations strongly implicate the brain RAS as an attractive target for the treatment of stress- and anxiety-associated cardiovascular disorders, and clinical trials are exploring the therapeutic potential of central nervous system (CNS) permeable angiotensin converting enzyme (ACE) inhibitors and ARBs (1, 42). ANG-(1–7), a RAS peptide opposing many of the actions of ANG II and responsible for many of the beneficial effects of ACE inhibition or ANG receptor blockade (37), may decrease anxiety (12). Whether the effects of ANG II or ANG-(1–7) on stress and cardiovascular reactivity are due to peripheral vs. central actions of the peptide, or some combination of the two, is unclear. However, there is a clinically established association between stress and increased cardiovascular risk (30, 49, 58). Thus the present review focuses on understanding the contribution of endogenous brain ANG peptides to modulation or mediation of the cardiovascular responses to several different types of stressors, highlighting studies in a unique transgenic rat model of targeted “underexpression” of the glial RAS (72).

THE BRAIN RAS AND CARDIOVASCULAR REGULATION

All components of the RAS are widely distributed in brain, independent from the circulating system (52, 62). The brain RAS components are expressed in neuronal and glial elements,
vascular elements, choroid plexus, and ependymal cells lining the ventricles. Evidence exists for an intracellular neuronal classical transmitter system and an extracellular more diffuse neuromodulator system (22), in addition to communication between these elements and circulating peptides via circumventricular organs or through paracrine mediators across the vascular wall-blood-brain barrier (61). The brain RAS is intimately involved in cardiovascular regulation through actions at receptors highly expressed at each relay of the sympathetic and parasympathetic nervous system synaptic circuitry including the paraventricular nucleus (PVN), rostral ventrolateral medulla (RVLM), and solitary tract nucleus (NTS) (4). In addition to local formation in discrete brain regions, circulating ANG peptides interact with the CNS through receptors localized to circumventricular organs deficient in a functional blood-brain barrier (6, 62). The cardiovascular actions of ANG II mediated through brain mechanisms include AT1 receptor-mediated stimulation of sympathetic outflow, release of catecholamines and neuroendocrine hormones, as well as impairment of baroreceptor actions that serve to restrain sympathetic input to the heart and vasculature (4, 52, 62). Blockade of ANG II actions with ACE inhibitors or ARBs specifically in the brain lowers blood pressure and improves baroreceptor reflex function in animal models of hypertension (60, 63). These therapies also increase levels of ANG-(1–7), a peptide that generally opposes the vasoconstrictor, profibrotic, and baroreceptor inhibitory ANG II actions (67, 80), suggesting that the balance of these two peptides is important for central cardiovascular regulation. Indeed, a peptide imbalance with increased ANG II and reduced ANG-(1–7) is evident in numerous pathophysiological conditions (24, 80). However, in brain areas such as the NTS, PVN, and RVLM, the two peptides may have common actions on other transmitter systems (vasopressin, substance P; see Refs. 23, 54, 71) and can produce similar increases in mean arterial pressure (MAP) related to acute and chronic stress stimuli (17, 25, 26, 50, 51, 78). This was illustrated in studies where nonselective ANG peptide antagonists, or either AT1 or ANG-(1–7) receptor antagonists injected into the RVLM prevented the MAP increase, but interestingly not the tachycardic response to air-jet stress or stimulation of the PVN (32, 50). These findings collectively reveal an important role for the brain RAS in cardiovascular regulation under normal conditions and in the context of cardiovascular-related diseases; however, as with any neurotransmitter/modulator system, the specific actions are dictated by the pathways involved.

As recently reviewed (1, 50, 64, 83), brain ANG II is also involved in modulation of cardiovascular responses to stress via actions at AT1 receptors widely distributed to organs of the HPA axis (4–7). The circulating ANG II response is dependent on the type and duration of stress and the level of activation of the RAS at the time of stress (43, 44, 84). The introduction of stress that stimulates the sympathoadrenal system increases renal renin release, plasma and brain ANG II levels, and central expression of AT1 receptors in brain regions involved in cardiovascular control. The resulting activation of the RAS promotes secretion of numerous stress hormones to further enhance sympathetic outflow and elevate MAP. Hypertensive rats with overactivity of the brain and adrenal RAS exhibit increased urinary levels of corticosterone and enhanced neuroendocrine responses to either ANG II or ACTH stimulation (38, 69). The effects of ANG II from either brain or peripheral sources can be mitigated by chronic central AT1 receptor blockade, suggesting that receptors within the brain are required for initiation of cardiovascular stress responses (50, 64, 65). However, these drugs have only been given for relatively short periods and may bind ubiquitous sites in the periphery, circumventricular organs, and brain for effects. In addition, there are reports that hypertensive rats with chronically elevated brain ANG II exhibit reduced release of vasopressin in response to exogenous administration of ANG II into hypothalamic sites (54). More compelling evidence for the obligate role for the PVN in the pressor response to circulating ANG II comes from studies employing adenoviral vector transfer of AT1a small hairpin RNA to the PVN. Knockdown of the AT1a receptor in the PVN markedly attenuated the acute increase in MAP by intravenous ANG II (59). The development of genetic technologies has led to the creation of transgenic rats with specific disruptions in the brain RAS to more specifically assess the role of central ANG II (5, 7). In particular, the transgenic ASrAOGEN rat developed by Bader and colleagues (72) with targeted disruption of glia-derived angiotensinogen in brain has been an important tool to study the contribution of this cellular source of the brain RAS to resting cardiovascular function and responses to stress.

EFFECT OF GLIA-SPECIFIC BRAIN RAS DISRUPTION ON RESTING CARDIOVASCULAR FUNCTION

The transgenic ASrAOGEN rat was created by insertion of an antisense oligonucleotide to angiotensinogen into the Sprague-Dawley rat germ line (72). The antisense oligonucleotide is driven by a glial fibrillary acidic protein promoter to specifically disrupt production from glial cells, the primary source of angiotensinogen in brain. As a result, these animals exhibit ≥90% reduction of angiotensinogen protein levels in brain and have lower hypothalamic tissue levels of ANG I, with a similar trend for ANG II (28, 34, 72). Providing validation for brain-specific targeting of the precursor protein, these animals have a normal circulating RAS but reduced drinking responses to central renin administration (72). In terms of the cardiovascular phenotype, conscious ASrAOGEN rats exhibit modest reductions in resting blood pressure and heart rate, to a degree similar to that seen with intracerebroventricular AT1 receptor blockade in a normotensive animal (60, 72). The improvement in cardiovascular function is largely attributed to the reduction in brain angiotensinogen and subsequent loss of glia-derived ANG II. However, ASrAOGEN rats also have lower levels of plasma vasopressin and altered central vasopressinergic pathways, which may contribute to the hypotension, lower body weights, and improved energy metabolism (14, 39, 41, 57, 68, 72). While the reduction in resting pressure may suggest reduced sympathetic activation (28), pharmacological testing shows increased parasympathetic, with no difference in sympathetic, tone to the heart in conscious animals (13). This selective improvement in parasympathetic tone is consistent with the higher heart rate variability and baroreceptor reflex sensitivity for both heart rate and sympathetic control in these animals, and mimics the CNS effects of ACE inhibitors and ARBs in normotensive and hypertensive rats (10, 13).
CARDIOVASCULAR RESPONSES TO PSYCHOEMOTIONAL STRESSORS IN ASRAOGEN RATS

The introduction of stress increases secretion of renin into the circulation and elevates both peripheral and central ANG II levels (1, 46, 50, 64, 83). Acute and chronic stress also increases AT\textsubscript{1} receptor density in cardiovascular brain regions with access to circulating ANG II including the PVN, subfornical organ, median eminence, and anterior pituitary. In response to stress, ANG II activates upregulated AT\textsubscript{1} receptors to stimulate release of ACTH, corticotrophin-releasing hormone (CRH), catecholamines, and adrenal corticoids. This neuroendocrine response further stimulates sympathetic outflow to promote elevations in blood pressure and heart rate. Central chronic administration of ARBs attenuates stress-induced increases in blood pressure, heart rate, and sympathetic outflow in animals, indicating a role for endogenous brain ANG II in stress reactivity (50). Interestingly, previous studies show that ANG II is only involved in stress-induced sympathetic activation in response to psychoemotional but not physical stress, suggesting inherent variability depending on the type of stressor (50). Moreover, the type and duration of stress can result in variable increases in circulating vs. CNS levels of ANG II (65).

Recent studies have employed transgenic ASRAOGEN rats to examine the effects of long-term disruption of the brain RAS on neuroendocrine and cardiovascular responses to psychoemotional stressors. Hypertensive rats have increased responses to stress stimuli (38, 69). Conversely, AT\textsubscript{1} receptor knockout mice have reduced blood pressure responses to aversive stressors (18). These findings suggest that endogenous ANG II is necessary for the initiation of cardiovascular responses to stress. It would be expected that ASRAOGEN rats, with downregulation of the brain RAS, have attenuated cardiovascular responses to stress. Although there are no differences in adrenal weight or basal levels of stress-related hormones, ASRAOGEN rats show increased corticosterone responses to CRH or ACTH stimulation and an upregulation of adrenal melanocortin-2 receptors compared with control animals, suggesting enhanced sensitivity to stimuli that activate adrenal pathways (56). In addition, ASRAOGEN rats respond with greater increases in pressure to ANG II given intracerebroventricularly (53). These enhanced responses may be in part due to the upregulation of AT\textsubscript{1} receptors in cardiovascular brain regions and associated increased sensitivity to ANG II observed in ASRAOGEN rats (9, 16, 40, 53). In contrast, studies by Baltatu and colleagues (8) show that ASRAOGEN rats have attenuated pressor responses and renin release after acute periods of restraint stress. Another study finds no differences in pressor responses to air-jet stress between ASRAOGEN and Sprague-Dawley rats (82). The variability in responses may suggest dependence on the type and duration of the stressor, in particular whether there is a sustained increase in circulating peptides that might access the increased AT\textsubscript{1} receptors in PVN. Stress stimuli can also produce different patterns of cardiovascular and neuroendocrine activation that are site and pathway specific. These collective findings suggest that the relationship between the endogenous brain RAS and cardiovascular responses to stress and associated mechanisms remains unclear, and more systematic research is needed using rigorously defined stress paradigms.

CARDIOVASCULAR RESPONSES TO SURGERY/ANESTHESIA STRESS IN ASRAOGEN RATS

Although conscious ASrAOGEN rats exhibit improved cardiovascular function, anesthetized animals have a paradoxical elevation in resting pressure and exaggerated responses to phencylbiguanide-induced activation of cardiac vagal chemosensitive fibers (2, 3, 27, 67). The effects of anesthesia on resting heart rate are less clear, as studies have reported lower, similar, or higher values in anesthetized ASrAOGEN relative to control rats depending on the type and dose of anesthesia used (2, 3, 14, 16, 28, 67). These findings may suggest differential activation of sympathetic outflow to organs involved in cardiovascular control under anesthesia in these animals (48, 74). To determine whether autonomic mechanisms underlie the anesthesia-induced elevation in pressure, we employed established pharmacological methods to discern the sympathetic and parasympathetic contributions to autonomic cardiovascular control in urethane/chloralose ASrAOGEN relative to Sprague-Dawley rats. The ganglionic blocker hexamethonium produced significantly greater depressor responses in anesthetized ASrAOGEN rats, despite achieving a similar level of MAP (Fig. 1). In contrast, there were no significant differences in intrinsic heart rate or sympathetic and parasympathetic tonus to the heart in anesthetized ASrAOGEN rats (unpublished data). These findings suggest that the elevated pressure is largely dependent on sympathetic activation to the vasculature (70), with little effect on autonomic control of the heart. Our data are consistent with the higher blood pressure variability, an indirect measure of sympathetic tone to the vessels, and preserved indices of vagal function including heart rate variability and baroreflex sensitivity for control of heart rate in ASrAOGEN rats under anesthesia (2, 3, 16, 67). In further support of maintenance of vagal tone in these animals, magnetoencephalography spectroscopy in isoflurane-anesthetized ASrAOGEN rats reveals higher levels of glutamate, a neurotransmitter critical for baroreflex function, in the dorsal medulla relative to normotensive and hypertensive rats (27). Overall, these findings provide evidence that targeted disruption of glia-derived angiotensinogen may result in increased susceptibility to stressors that induce increases in brain or circulating ANG II, leading to greater sympathetic activation to promote elevations in resting MAP. As further evidence for enhanced cardiovascular responses to acute stress in ASrAOGEN rats, these animals maintain MAP during hemorrhage at a level which produces hypotension in Sprague-Dawley rats (15, 19, 20). Moreover, ASrAOGEN animals exhibit increases in resting MAP in response to chronic metabolic stress induced by hypercaloric diet that has no effect on MAP in Sprague-Dawley rats (15, 19).

POTENTIAL MECHANISMS PARTICIPATING IN ANESTHESIA-INDUCED PRESSOR RESPONSES IN ASRAOGEN RATS

The increase in sympathetic outflow in response to anesthesia in ASrAOGEN rats may be due in part to activation of the RAS, at either peripheral or central sites of action. Anesthetics in general are known to increase plasma renin activity and levels of circulating ANG II in normotensive and hypertensive rats, although the magnitude of increase may vary with type of agent and duration of treatment (33, 35, 75). Evidence for a
ANG peptide levels to a similar extent in SD and ASrAOGEN rats. *P < 0.05 versus conscious using independent t-test.

Fig. 1. Depressor responses to ganglionic blockade. Depressor responses to ganglionic blockade induced by intravenous infusion of the N Ch nicotinic receptor antagonist hexamethonium (40 mg/kg) were determined for individual urethane/α-chloralose anesthetized Sprague-Dawley (SD) and ASrAOGEN rats. To assess for differences between SD (n = 11) and ASrAOGEN rats (n = 12), data were pooled for each strain and presented as means ± SE and represent circulating ANG peptide levels (pg/ml) assessed from trunk blood of naïve conscious and combination urethane and hypoxic stress-induced hypertension lowers MAP (17, 25, 26, 50, 51, 78). Of interest is the observation that ANG peptides from glial vs. neuronal cells can participate in different components of cardiovascular regulation (55, 66). Because glia-derived angiotensinogen is reduced in ASrAOGEN rats (72), ANG peptides from a nonglial source likely contribute to the pressor responses to anesthesia. We propose three possibilities for the nonglial sources of ANG peptides in ASrAOGEN rats that may contribute to the increase in MAP under anesthesia: 1) neuron-derived, 2) circulating, and 3) both neuron-derived and circulating. Although astrocytes are the primary source of angiotensinogen in brain, this precursor is also expressed in neurons (76, 79). Consistent with neuronal expression of angiotensinogen in brain, preliminary studies (Fig. 2) indicate that ANG II and ANG-(1–7) immunoreactivities are preserved in the PVN and medullary autonomic centers (9, 11, 25, 78). These pathways can subsequently stimulate sympathetic outflow and renin release, illustrating a positive feed-forward circuit which may contribute to the acute pressor actions of ANG II. Indeed, angiotensinergic neuronal circuits among these cardiovascular nuclei are implicated in several aspects of cardiovascular control, including resting autonomic reflex function as well as sympathoexcitatory responses to stress, congestive heart failure, and hypertension (11, 32).

In anesthetized ASrAOGEN rats, circulating ANG peptides are elevated to a similar extent as in Sprague-Dawley animals (Table 1). However, AT1 receptors are elevated in key cardiovascular nuclei (40, 53), accompanied by an increased sensitivity to the pressor effects of ANG II microinjection in these animals (9, 16). The anesthesia-induced elevation in ANG II may therefore precipitate exaggerated activation of descending angiotensinergic pathways. Moreover, stress-related activation of descending pathways from the PVN can occur without stimulation of the circulating RAS (11). Increased activity of the vasopressinergic system also plays an important role in cardiovascular responses to acute and chronic stress in animals (77). The same mechanisms appear to be involved in the potentiation of cardiovascular responses to stress by brain ANG and vasopressin systems. Although ASrAOGEN rats have reduced plasma and hypothalamic vasopressin levels, these animals have increased vasopressin V1a receptors in the brain stem relative to control rats associated with increased sensitivity to the cardiovascular effects of NTS microinjection of vasopressin (14, 72). The extent to which elevations in ANG II or vasopressin contribute to the enhanced responses to hypercaloric diet and hemorrhage in ASrAOGEN rats remains to be determined.

Providing evidence for an enhanced central role of ANG peptides in the support of resting blood pressure under anesthesia in ASrAOGEN rats, NTS administration of either ANG II or ANG-(1–7) receptor antagonists normalizes pressure (2, 67). Although endogenous ANG II and ANG-(1–7) have opposing actions on baroreflex function (67), both peptides may mediate responses to stress in the RVLM or PVN, injection of either peptide evokes similar pressor responses in these areas, and the ANG-(1–7) antagonist injected into the PVN of animals with hypoxic stress-induced hypertension lowers MAP (17, 25, 26, 50, 51, 78). Of interest is the observation that ANG peptides from glial vs. neuronal cells can participate in different components of cardiovascular regulation (55, 66). Because glia-derived angiotensinogen is reduced in ASrAOGEN rats (72), ANG peptides from a nonglial source likely contribute to the pressor responses to anesthesia. We propose three possibilities for the nonglial sources of ANG peptides in ASrAOGEN rats that may contribute to the increase in MAP under anesthesia: 1) neuron-derived, 2) circulating, and 3) both neuron-derived and circulating. Although astrocytes are the primary source of angiotensinogen in brain, this precursor is also expressed in neurons (76, 79). Consistent with neuronal expression of angiotensinogen in brain, preliminary studies (Fig. 2) indicate that ANG II and ANG-(1–7) immunoreactivities are preserved in

Table 1. Circulating levels of ANG peptides in response to anesthesia

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<th>SD</th>
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<td></td>
<td>Conscious</td>
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<tr>
<td>ANG I</td>
<td>101 ± 13</td>
<td>1,067 ± 214*</td>
<td>88 ± 16</td>
<td>658 ± 66*</td>
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<tr>
<td>ANG II</td>
<td>27 ± 4</td>
<td>243 ± 35*</td>
<td>10 ± 7</td>
<td>207 ± 29*</td>
</tr>
<tr>
<td>ANG-(1–7)</td>
<td>13 ± 4</td>
<td>59 ± 5*</td>
<td>16 ± 5</td>
<td>83 ± 13*</td>
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Values are means ± SE and represent circulating ANG peptide levels (pg/ml) assessed from trunk blood of naïve conscious and combination urethane and α-chloralose (750 and 35 mg/kg, respectively) anesthetized Sprague-Dawley (SD; n = 8–17) and ASrAOGEN rats (n = 6–9). Anesthesia significantly increased ANG peptide levels to a similar extent in SD and ASrAOGEN rats. *P < 0.05 versus conscious using independent t-test analysis.
Fig. 2. Neuronal localization of ANG II and ANG-(1–7) in the paraventricular nucleus (PVN): comparison of SD and ASrAOGEN rats. Coronal brain sections (18 μm) from 3 SD and 3 ASrAOGEN rats were processed (fixed with 4% paraformaldehyde) and cryoprotected in 20% sucrose for 2 days. Frozen sections were cut with a cryostat and collected into PBS. The precise anatomical location was determined using Nissl stained sections. For fluorescence, adjacent sections were blocked in 2% normal serum in PBS plus 0.3% Triton-X for 1 h, then placed in primary antibody overnight at 4°C. After they were rinsed, the sections were further reacted for 30 min in the appropriate fluorophore-conjugated secondary antibody (Jackson ImmunoResearch Laboratories, West Grove, PA) at 1:500, rinsed, mounted on subbed slides, coverslipped with anti-fade mounting media, and viewed either on Nikon Optiphot equipped for fluorescence or a Zeiss confocal microscope.

A: representative confocal images of ANG-(1–7) immunoreactivity [anti-ANG-(1–7) provided by Dr. Mark Chappell; green CY2] showed double labeling with NeuN (Chemicon anti-NeuN, 1:500; red CY3; Chemicon International, Temecula, CA) in the PVN of both SD and ASrAOGEN rats. This is illustrated by the yellow nuclei in almost all cells staining green with the ANG-(1–7) antibody. In contrast, there is no colocalization with glial fibrillary acid protein (GFAP; Sigma-Aldrich (St. Louis, MO) anti-GFAP at 1:1,000; red CY2) as the green and red remain distinct with no yellow staining.

B: although not as robust as the ANG-(1–7) staining, ANG II immunoreactivity (Peninsula anti-ANG II at 1:200; Peninsula Laboratories, San Carlos, CA; red) was observed in the PVN of both SD and ASrAOGEN rats. There is no difference in the extent of staining between strains (top panels). We further show that ANG II (red) immunoreactivity is colocalized (arrows) with ANG-(1–7) (green) in the PVN, as indicated by the yellow staining in cells identified by white arrows. There is separation of staining for ANG II (green) and GFAP (red) in the PVN, as no yellow staining is observed, indicating ANG II localization within neuronal and not glial elements.
neuronal pathways of the PVN of ASrAOGEN relative to Sprague-Dawley rats (81). The data in Fig. 2 illustrate three important concepts: 1) ANG II and ANG-(1–7) are colocalized in PVN neurons, 2) both peptides are associated primarily with neuronal markers in this brain area, and 3) there is no apparent difference in peptide content in Sprague-Dawley and ASrAOGEN rats. Thus, while the loss of glial angiotensigen appears to upregulate AT1 receptors in brain cardiovascular areas including the PVN, the neuronal ANG peptide content remains intact, consistent with the interpretation that neuronal pathways containing both ANG peptides projecting from PVN to NTS and RVLM contribute to setting the resting level of MAP under conditions of anesthesia. In contrast, glia-derived ANG II attenuates baroreflex sensitivity in younger and older anesthetized ASrAOGEN rats (2, 67), whereas a non-glial source of ANG-(1–7) contributes to the preservation of baroreflex function in these animals. Overall, the current data support the concept that alterations in glia-derived ANG peptides influence the response to acute activation of neuronal pathways, perhaps as a result of regulation of AT1 receptors in brain centers regulating autonomic function.

COMPARISON TO TRANSGENIC ANIMALS WITH OVEREXPRESSION OF THE REN2 GENE

While not exactly opposite to ASrAOGEN rats, the phenotype of the (mRen2)27 transgenic rat with overexpression of the mRen2 gene is worthy of mention, in view of the response patterns presented in the preceding sections for the animals with low brain angiotensigen. The (mRen2)27 rats are hypertensive with impaired baroreflex sensitivity, likely resulting from a deficiency in medullary ANG-(1–7) (21, 36, 73). Hypothalamic tissue levels of ANG peptides are reportedly high in these animals (45, 73), but, rather than a targeted overexpression in brain, there is also excess ANG II in adrenal glands and probably in the circulation (72). While these animals have normal apparent receptor density in the PVN (40), there is evidence of desensitization of hypothalamic responses to ANG peptides for vasopressin release as well as pressor responses (23, 54). Interestingly, (mRen2)27 transgenic rats exhibit a reduction in blood pressure to normotensive levels in response to anesthesia and larger reductions in MAP with hemorrhage than the ASrAOGEN rats (20, 21, 47). In view of the findings in the ASrAOGEN rats, where higher AT1 receptors in the PVN are associated with increased reactivity to several different types of stress, particularly those that may be associated with elevated circulating or brain ANG II, it is possible that the reduction in pressure under anesthesia or hemorrhage stress in the (mRen2)27 hypertensive rats is a result of desensitization of the receptors in PVN, and failure to increase circulating ANG II to sufficiently activate descending pathways involved in the response to this stressor. The validity of this interpretation remains to be assessed.

CONCLUSIONS

It is well established that increased cardiovascular reactivity to stress is a significant predictor of hypertension and other cardiovascular diseases (30, 49, 58). The majority of evidence from animal studies suggests that overactivity of the brain RAS contributes to enhanced responses to psychoemotional stressors and that blockade of ANG II actions within the brain may be a novel target to disrupt neuroendocrine and cardiovascular stress responses for the treatment of stress-related disorders (1, 42, 50, 64). The stress-induced stimulation of the RAS appears to be dependent on the type and duration of stressors as well as on peripheral vs. central sites of action. However, genetic disruption of the endogenous glial RAS, as observed in transgenic ASrAOGEN rats, results in preserved neuronal peptides in stress-related pathways. An associated upregulation of ANG receptor density in these pathways may account for the exaggerated cardiovascular responses to stress stimuli associated with ANG II activation including anesthesia and possibly psychoemotional stressors. However, there is not a uniform exaggeration of pressor responses to all stressors in these animals, and further studies more closely evaluating the degree of elevation of circulating angiotensin peptides vs. brain peptides, and the accompanying changes in other neurohumoral factors, is required. Nevertheless, further studies to determine the consequence of long-term systemic ANG II blockade on cardiovascular reactivity in response to stress are warranted given the success of recent trials in posttraumatic stress.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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