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Aging and the brain renin-angiotensin system:

relevance to age-related decline in cardiac function

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Abstract

This article discusses evidence that impairments in control of autonomic outflow mediated by the brain renin-angiotensin system (RAS) contribute to the decline in baroreceptor reflex function and the development of insulin resistance that accompany hypertension and excess salt intake, especially during aging. Imbalances in the regulation of the sympathetic and parasympathetic limbs of the autonomic nervous system observed in older subjects underlie changes in heart-rate variability and play a role in the regulation of overall cardiac function. Age-related alterations in autonomic nervous system function may also explain the age-associated alterations in metabolism. Reduced heart-rate variability is linked to increased mortality in patients with cardiovascular disorders and, coupled with information that is known about local changes in the cardiac and brain RAS during aging, the evidence reveals potential mechanisms for the protective effects of systemic blockade of the RAS against age-related changes that impact the heart.

Executive summary—

- Disturbances in the brain renin-angiotensin system as a result of aging or conditions of excess salt contribute to imbalances in autonomic nervous system function leading to impairments in baroreceptor reflex control of heart rate and energy metabolism.
- Cardiac structural and functional abnormalities, both systolic and diastolic, may result as a component of their etiology, the age-related hypertension and accompanying baroreflex, insulin resistance or bodyweight changes that are secondary to the impaired autonomic function resulting from alterations in the brain renin-angiotensin system.
- Reductions in Ang-(1-7) in tissues such as brain or heart during the aging process or other conditions such as excess salt intake, rather than frank increases in Ang II, appear to contribute to pathophysiologic changes in cardiac structure and function.

Keywords

baroreceptor reflex; brain; cardiac function; diastolic function; insulin resistance; renin-angiotensin system; salt sensitivity

Manifestations of cardiovascular aging frequently include the development of systolic hypertension, central arterial stiffness and cardiac diastolic dysfunction. Aging is associated with marked changes in cardiac structure, such as cardiomyocyte loss, hypertrophy of remaining cells and the development of fibrosis [1,2]. Importantly, dietary salt excess has been shown to be an invariable determinant of the age-related changes in blood pressure and end-organ damage in many clinical and experimental studies. A large body of epidemiological and experimental evidence demonstrates a significant association between high salt intake and blood pressure as well as a rise in systolic and diastolic blood pressure with aging [3-5]. While these changes are presumed to be a major reason for the altered diastolic compliance of the senescent heart, age-related increases in arterial stiffness can further lead to vascular-ventricular uncoupling [6,7], which, when taken together, predispose to diastolic heart failure (DHF). Stimuli for this cardiovascular remodeling associated with aging and diastolic heart disease include hypertension, increases in bodyweight gain, insulin resistance and renal dysfunction [8]. A common feature associated with the conditions of excess salt or advanced age is impairment of the baroreceptor reflexes for control of heart rate. Reduced heart-rate variability accompanies the imbalance in the sympathetic and parasympathetic nervous system that contributes to reduced reflex function and both can be linked to the structural and humoral changes associated with aging. The role that the brain renin-angiotensin system (RAS) is thought to play in the changes responsible for cardiac aging is discussed below.

Brain RAS, baroreflex & autonomic dysfunction during aging

There is a close anatomical association in brain and periphery of the RAS with both sympathetic and parasympathetic limbs of the autonomic nervous system [9]. Long-term RAS blockade extends the lifespan and improves or prevents the age-related decline in cardiovascular and metabolic function in hypertensive rats as might be expected, but treatment of normotensive rats attenuates the age-related decline in cognitive function, the increase in bodyweight gain and decline in mitochondrial function, and preserves renal function [10-16]. Numerous studies, however, report a decrease in the plasma RAS components with increased age [17-19], which raises issues regarding whether RAS blockade of a variety of local tissue RAS (brain, kidney, heart, pancreas, adipose and adrenal) contributes to the improvements observed [20,21]. Little is known about the regulation of the local RAS, specifically, the levels of Ang II and Ang-(1-7), within each tissue during aging. There may be an overt elevation of components of the system, as reported for Ang II in the heart during aging [19], consistent with observations on the intrarenal RAS [14,16-18]. In experimental models, increases in gene expression of angiotensinogen, angiotensin-converting enzyme (ACE), Ang II type 1 (AT₁) and Ang II type 2 (AT₂) receptors have been identified in hearts from senescent rats, independent of circulating RAS [22,23]. Blockade of the RAS by either ACE inhibition or AT₁-receptor blockers prevents the increase in urinary Ang II in several studies [14,16]. However, these treatments not only reduce the levels or actions of Ang II, but also cause an associated elevation in the levels or actions of Ang-(1-7), another active component of the RAS that has actions that oppose those of Ang II. These complex interactions are illustrated in Figure 1. Therefore, the exact mechanisms responsible for improvements in age-related dysfunctions with RAS blockade are not completely understood and recent studies reveal that maintenance of healthy levels of Ang-(1-7) may be part of the mechanisms of the cardiovascular protection.

The nucleus of the solitary tract (nTS) in the dorsal medulla oblongata is a known site for the actions of Ang II to reduce the sensitivity of the baroreceptor reflex control of heart rate, a vagally mediated component of the reflex control of arterial pressure [24,25]. Endogenous Ang-(1-7) counterbalances the actions of Ang II on the baroreflex within the nTS as shown in Figure 2. In Sprague-Dawley (SD) rats, there is an increase in systolic blood pressure during aging that is associated with increased bodyweight gain, higher circulating insulin and leptin levels [26] and impairment of the baroreflex to levels similar to those seen in overt hypertension [27]. The facilitation of the reflex by endogenous Ang-(1-7) is absent in the older SD rats [27]. By contrast, the response to blockade of endogenous Ang II by an AT₁-receptor antagonist is similar between older and younger SD rats [27]. Preliminary data suggest that expression and activity of the two Ang-(1-7)-forming enzymes (neprilysin and ACE2) are lower in brain medulla of older SD rats [27,28], which, if confirmed, would provide a mechanism for reduced endogenous Ang-(1-7) in older animals. Acute ACE2 inhibition in the nTS is associated with a reduction in baroreflex sensitivity for control of heart rate in young SD rats [29]. Thus, low levels of Ang-(1-7) in the nTS may contribute to the age-related imbalance in sympathetic and parasympathetic control of heart rate, and the possibility that its preservation in older animals contributes to the mechanism of action of ACE inhibitors or AT₁-receptor blockers should be considered for the protective effects of these agents. The loss of baroreflex sensitivity may result in reduced heart-rate variability and increased blood pressure variability, and subsequent cardiac structural changes even in the absence of established hypertension, leading to cardiac function impairments.

Ang II receptors in brainstem nuclei parallel the distribution of the entire vagal sensory and motor pathways, and are not confined to the cardiopulmonary system [25,30,31], consistent with a widespread influence of the RAS on autonomic function [9,32]. It is not yet clear whether the other age-related changes in autonomic function that accompany the impaired baroreflex and that are associated with decreased heart-rate variability can be linked to changes in Ang-(1-7) in the medulla. However, these same brain areas are those involved in the control of appetite and body energy metabolism [33-37]. To better understand the specific role of the brain RAS in the aging process with respect to metabolic and cardiovascular function, our recent studies compared SD rats with transgenic rats that have a deficiency in brain angiotensinogen (ASrAogen). The ASrAogen transgenic rats have a GFAP promoter-linked angiotensinogen antisense sequence overexpressed in brain glia [38], thereby selectively targeting the main source of angiotensinogen and reducing cerebral levels of the prohormone to less than 10% of normal [38,39]. ASrAogen-deficient rats have slightly lower values of resting arterial pressure, but otherwise exhibit similar circulating levels of leptin, insulin and glucose values in early adulthood [26]. ASrAogen rats do not, however, exhibit increases in systolic pressure, insulin or leptin during aging [26], and have a longer lifespan [40,41]. In older ASrAogen rats, actions of Ang-(1-7) to facilitate baroreceptor reflex control of heart persist [42], indicating that both metabolic function and other indices of autonomic health are maintained in these animals. In fact, circulating levels of Ang-(1-7) are significantly higher in older ASrAogen rats than age-matched SD animals [18], and it is known that long-term systemic infusions of Ang-(1-7) improve baroreflex function [43]. All of the above features of the older ASrAogen animals are comparable with rats who have lifetime RAS blockade [10, 13]. Surprisingly few studies have, however, assessed levels of angiotensin peptides or other RAS components in the brain during aging. The concept that the brain RAS is elevated with advanced age, and that blockade of the brain RAS specifically accounts for a part of the protective mechanisms of systemic RAS blockade, is currently under investigation. In fact, a recent study in hypertensive human subjects suggests that ACE inhibitors that cross the blood-brain barrier are more likely to preserve cognitive function in the elderly than other antihypertensive agents [44]. Whether ACE inhibitors with these characteristics would exhibit greater protection for cardiac and other cardiovascular and metabolic function during aging is an intriguing possibility that has not yet been established.

Brain RAS, cardiac aging & salt excess

Many interventional trials confirm that salt reduction successfully decreases arterial pressure not only in hypertensive, but also in normotensive subjects [45-47]. Since the increase in systolic blood pressure and reduced compliance of large arteries are frequent observations in cardiovascular aging, it is without surprise that left ventricular hypertrophy and fibrosis, and impairments in ventricular performance and coronary hemodynamics, are common findings in aging [48,49]. Importantly, studies from our laboratory provide evidence that in normotensive Wistar-Kyoto (WKY) rats fed a high salt diet from 20 to 60 weeks of age exhibit increases in arterial pressure and severely compromised coronary hemodynamics, promoting the development of heart disease [50]. These changes mimic age-related cardiovascular alterations in senescent WKY rats [51], providing strong evidence that dietary salt excess accelerates cardiovascular aging. Similar changes were evoked in both young adult and old spontaneously hypertensive rats (SHRs), a well-characterized model of essential hypertension in humans [52,53]. As seen in older WKY rats, salt-loaded SHRs manifest impaired left ventricular relaxation and preserved systolic function associated with enhanced fibrosis, a frequent observation in hypertensive and elderly patients. In addition, similar changes in fibrosis, function and coronary hemodynamics occur in the right ventricle of salt-loaded SHRs, a chamber that is not subjected to increased afterload resulting from high salt intake [53]. These findings strongly suggest that, besides affecting blood pressure, salt exerts additional nonhemodynamic cardiac effects. Indeed, several large epidemiological studies indicate that dietary salt excess is a strong and even independent contributor to increased cardiovascular risk and mortality [54,55]. Consistently, increased salt intake appears to be a critical independent predictor of left ventricular enlargement in patients with essential hypertension [56,57]. Moreover, in hypertensive patients challenged with high sodium intake, early abnormalities in left ventricular diastolic function are seen in sodium-sensitive but not in sodium-resistant subjects, despite similarities in basal blood pressure between the two groups [58].

Various nonhemodynamic mechanisms have been suggested to explain detrimental cardiovascular effects of salt excess. Thus, the function of the sympathetic nervous system, the interaction between different vasoactive hormones and growth factors and even the direct effects of sodium *per se* have been extensively studied in various experimental models of salt-sensitive hypertension [59-63]. In particular, the pathophysiological role of the RAS in salt-sensitive hypertension has been increasingly appreciated in recent years. Despite the fact that in response to high sodium intake a suppression of circulating RAS should occur [59,62,63], by contrast, an inadequate suppression or even paradoxical activation of local tissue RAS has been described. In fact, recent findings suggest a suppression of cardiac Ang-(1-7) in the face of elevated or maintained levels of Ang II resulting from decreases in ACE2 expression [64]. This imbalance in the two peptides may favor actions of Ang II locally within the heart. Long-term treatments with Ang-(1-7) protect the heart from global ischemia in situations of low nitric oxide hypertension and diabetes in normotension and hypertension, and endogenous Ang-(1-7) may contribute to the protection observed with RAS blockade [65-67]. The common theme for healthy cardiac function may, therefore, include preservation of Ang-(1-7), similar to what was previously mentioned with respect to the brain RAS during aging.

The mechanisms of high salt-induced impairments in cardiac function also include actions within the CNS. Chronic dietary salt intake results in sympathetic hyperactivity and pressor responses in salt-sensitive strains mediated through a brain ouabain-like substance and RAS [68-70]. Indeed, a high salt diet increased ACE mRNA and activity in the hypothalamus and pons of Dahl-sensitive rats [71], as well as AT₁-receptor binding in the paraventricular nucleus, median preoptic nucleus, and suprachiasmatic nucleus [72]. By contrast, chronic AT₁-receptor blockers given in the cerebral ventricles [68,69], median preoptic nucleus [73] or rostral

ventrolateral medulla [74] prevented sympathoexcitation and hypertension in salt-sensitive strains. Further implicating the brain in the generation of the salt sensitivity is the additional finding that the ASrAogen rats are protected from the hypertension induced by centrally administered ouabain [39]. There is a large body of evidence suggesting that salt excess activates local cardiac [75-78] and renal [63] tissue RAS as well. Thus, it appears that brain RAS, in concert with activated local tissue RAS in peripheral organs, could account, at least in part, for blood pressure increases as well as target-organ damage in salt-sensitive hypertension. Therefore, we speculate that the inappropriate activity of the local tissue (brain, heart and kidney) RAS, especially with respect to the balance between Ang II and Ang-(1-7), relative to the level of salt intake may account for the blood pressure rise and the cardiovascular and renal functional and structural changes in the elderly that are regularly considered as the 'physiological manifestation of aging'. An intriguing aspect of this concept is further compounded by data demonstrating that the neuron-specific expression of human angiotensinogen increased preference for salt in transgenic mice [79]. Clearly, further studies are warranted to confirm this attractive hypothesis.

Brain RAS, cardiac aging & diastolic dysfunction

Diastolic dysfunction, another common correlate of aging that has profound implications on functional abilities late in life, may also be linked, in part, to the brain RAS. In brief, diastolic dysfunction consists of abnormal myocardial relaxation and increased chamber stiffness induced by alterations in the cardiac calcium regulatory proteins and the extracellular matrix, respectively [80]. The age-related cellular and molecular alterations that contribute to diastolic impairment may represent adaptive, physiologic dysfunction (e.g., secondary to aortic stenosis or long-standing hypertension) or the other end of the clinical disease spectrum, DHF. Importantly, diastolic dysfunction is a mechanical abnormality (not a clinical syndrome) that occurs during diastole, which may or may not result in symptoms. By contrast, DHF is characterized by high left ventricular end-diastolic pressures due to abnormalities in left ventricular filling and neurohormonal regulation, which when taken together lead to pulmonary congestion, exercise intolerance and decreased life expectancy.

Indeed, diastolic dysfunction may antedate DHF since 11-15% of patients with asymptomatic diastolic dysfunction develop frank symptoms of heart failure within 5 years [81]. However, while numerous therapeutic and device strategies have been successfully instituted for the management of systolic heart failure [82], current treatment to prevent the worsening of diastolic dysfunction and/or reducing mortality has been empiric. This is partly owing to the fact that therapeutic studies with heart failure patients excluded elderly patients and patients with diastolic dysfunction with preserved systolic function. Another reason for the paucity of randomized treatment trials specifically addressing this syndrome is that we do not have a clear idea of the pathogenesis underscoring the disease process.

Aging is associated with marked changes in cardiac structure leading to the altered diastolic compliance observed in the senescent heart [6,7], yielding a predisposition to DHF. Hypertension, increases in bodyweight gain, insulin resistance and renal dysfunction are factors contributing to remodeling associated with aging and diastolic heart disease [8]. As mentioned above, increases in cardiac tissue components of the RAS occur in older rats [19,22,23]. Moreover, in patients with left ventricular hypertrophy, sub-systemic doses of intracoronary ACE inhibitors improve left ventricular filling, distensibility and regional relaxation [83]. Longer-term oral treatment with ACE inhibitors and AT₁-receptor blockers improve measures of diastolic function and functional capacity in hypertensive patients with left ventricular hypertrophy [84-86]. Although it is not entirely clear whether these effects translate into better clinical outcomes in older patients with heart failure with preserved systolic function, also known as DHF, findings from the Candesartan in Heart Failure Assessment of Reduction in

Mortality and Morbidity (CHARM)-Preserved trial [87] indicate that treatment with the AT₁-receptor blocker, candesartan reduces hospital admission for worsening heart failure. Certainly, findings from the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial of more than 4000 patients older than 60 years of age should provide more conclusive information regarding the primary end point of death [88].

Besides the local cardiac RAS, findings from animal studies suggest that activation of the brain RAS may also contribute to age-related left ventricular remodeling, diastolic dysfunction and heart failure. First, in studies involving heart failure due to myocardial infarction, heart-brain signaling via neurohumoral mechanisms has been shown to be an important determinant of left ventricular function and remodeling. Specifically, blockade of AT₁ receptors in the brain of rats subjected to coronary ligation reverses the sympathetic hyperactivity associated with heart failure [89]. Furthermore, chronic AT₁-receptor blockade or attenuation of brain ouabain-like activity (which also contributes to sympathetic hyperactivity associated with heart failure) substantially inhibits the development of left ventricular dilation and dysfunction in rats after myocardial infarction [90]. Consistent with these studies, Wang *et al.* demonstrated that the transgenic rats with low brain RAS (ASrAogen) due to suppression of the glial angiotensinogen gene, were protected from sympathetically induced left ventricular dysfunction and the increased fibrosis accompanying the remodeling after myocardial infarction [91]. Overall, these data suggest that the brain RAS, probably acting through the sympathetic nervous system, plays a substantial role in ventricular remodeling and myocardial dysfunction associated with ischemic heart failure. Lower activity of the brain RAS may protect the heart in pathological conditions normally associated with increased fibrosis, leading to the development of diastolic dysfunction.

In fact, to more specifically assess the role of Ang II locally produced in the brain in cardiac aging, we recently compared diastolic function among three groups of age-matched (12 months of age) rats with varying degrees of RAS activation, including [41]:

- Elevated peripheral and brain Ang II of the transgenic (mRen2)27 rat with overexpression of the mouse renin gene:
- Reduced brain and normal peripheral Ang II of the ASrAogen rat with low glial angiotensinogen:
- Normal brain and peripheral Ang II of the Hannover SD rat, the parent strain of both transgenics.

In brief, chronic overactivity of peripheral and brain RAS of the aging transgenic (mRen2) 27 rat was associated with hypertension (systolic blood pressure of 155 mmHg), increased cardiac fibrosis and reduced levels of the calcium regulatory protein, SERCA2, and was accompanied by accelerated systolic and diastolic dysfunction. By contrast, the age-matched ASrAogen rat with low brain RAS and normal peripheral Ang II exhibited low resting systolic blood pressure (107 mmHg), minimal cardiac fibrosis, relatively conserved SERCA2 content and preserved diastolic function when compared with the (mRen2)27 and the SD parent strain, manifesting mild hypertension (systolic blood pressure of 145 mmHg) and reduced exercise tolerance at this age. Taken together, these data support the concept that overactive brain RAS exacerbates diastolic dysfunction of aging, and that low brain RAS expression and its consequences may be protective against hypertension and DHF. Moreover, the ASrAogen model provides a valuable experimental tool for elucidating the potential role of central RAS blockade in the attenuation of cardiac aging.

Future perspective

Ongoing studies are designed to understand the precise neural pathways involved in the effects of the brain RAS on the age-related changes in autonomic function. Determining whether the same pathways mediate regulation of blood pressure and metabolism is warranted, given that data support the dissociation of the two in overall development of age-related pathologies. The preliminary studies cited above provide intriguing insights into factors that regulate expression of the prohypertensive, vascular injury components of the RAS leading to generation of Ang II in comparison with the vasculo-protective arm leading to Ang-(1-7) formation. Certainly, the recent observations that regulation of the balance between ACE and ACE2 may play a key role in the preservation of cardiovascular health provides rationale for the basis of future research into therapies to increase expression of ACE2, especially during aging, salt excess, cardiac failure or hypertension. We already recognize that systemic inhibition of the RAS achieves a shift in the balance of the system from Ang II to Ang-(1-7), with both the decline in Ang II and the increase in Ang-(1-7) accounting for cardio- and renoprotection during aging and development of cardiovascular diseases. In the future, we hope to provide a better understanding of the role of the brain RAS and control of autonomic system function as contributors to the development of age-related and other cardiovascular pathologies, and whether specific blockade of the brain RAS accounts for a major component of the improvements observed with systemic RAS blockade.

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Figure 1. Processing pathways and major components of the renin-angiotensin system

ACE: Angiotensin-converting enzyme: AT₁R: Ang II type 1 receptor: AT₂R: Ang II type 2 receptor: D-Ala: Ang-(1-7) *Mas* receptor antagonist [D-Ala⁷]-Ang-(1-7): NEP: Neprilysin: Sartans: AT₁R antagonists class agents including losartan, candesartan, irbesartan, olmesartan and valsartan.

Figure 2. Effect of endogenous angiotensin peptides on baroreflex function

Baroreflex sensitivity (BRS) in young (~15 weeks) and old (~70 weeks) Hannover Sprague-Dawley rats at baseline and after blockade in the solitary tract nucleus with either the AT₁-receptor antagonist CV (12 pmol/120 nl) or the Ang-(1-7) receptor antagonist D-Ala (144 fmol/120 nl). Older rats had significantly lower BRS than younger animals and the blockade with D-Ala had no effect on the BRS in the older rats.

CV: Candesartan; D-Ala: D-Ala⁷-Ang-(1-7).

Data taken from [27].