Heart failure and the brain: new perspectives

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Felder, Robert B., Joseph Francis, Zhi-Hua Zhang, Shun-Guang Wei, Robert M. Weiss, and Alan Kim Johnson. Heart failure and the brain: new perspectives. Am J Physiol Regul Integr Comp Physiol 284: R259–R276, 2003; 10.1152/ajpregu.00317.2002.—Despite recent therapeutic advances, the prognosis for patients with heart failure remains dismal. Unchecked neurohumoral excitation is a critical element in the progressive clinical deterioration associated with the heart failure syndrome, and its peripheral manifestations have become the principal targets for intervention. The link between peripheral systems activated in heart failure and the central nervous system as a source of neurohumoral drive has therefore come under close scrutiny. In this context, the forebrain and particularly the paraventricular nucleus of the hypothalamus have emerged as sites that sense humoral signals generated peripherally in response to the stresses of heart failure and contribute to the altered volume regulation and augmented sympathetic drive that characterize the heart failure syndrome. This brief review summarizes recent studies from our laboratory supporting the concept that the forebrain plays a critical role in the pathogenesis of ischemia-induced heart failure and suggesting that the forebrain contribution must be considered in designing therapeutic strategies. Forebrain signaling by neuroactive products of the renin-angiotensin system and the immune system are emphasized.

angiotensin; aldosterone; cytokines; tumor necrosis factor; immune system; renin; vasopressin; sympathetic; extracellular fluid volume; baroreflex

THE IMPORTANCE OF AUTONOMIC dysfunction to the progression of heart failure is firmly established (55, 113, 120, 152). The most effective treatments for heart failure specifically target the peripheral manifestations of neurohumoral activation (86, 113). Yet the understanding of the mechanisms leading to neurohumoral excitation in heart failure is still quite limited.

Over the last several decades, substantial evidence has been amassed to support the concept that peripheral afferent systems innervating the heart and vascular tree are altered in heart failure. Dysfunction has been described in all components of the reflexes mediated by these cardiovascular afferent systems—theafferent fibers themselves, the central processing of the afferent signals, the efferent innervation of the end organs, and the end organs themselves. In general, the influence of low- and high-pressure baroreceptors (40, 42, 191) that normally restrain sympathetic drive and vasopressin release is diminished, whereas the excitatory influences of arterial chemoreceptors (161) and cardiac sympathetic afferent fibers (100) are enhanced.

Central nervous system (CNS) neurons affecting cardiovascular regulation respond to humoral as well neural signals. Blood-borne neuroactive peptides, too large to readily cross the blood-brain barrier, may influence the brain by activating sensory neurons at specific sites in hindbrain and forebrain that lack a blood-brain barrier (15, 18) or by inducing the release of mediators that do penetrate the barrier (135). These neuroactive substances are released in excess by peripheral tissues under the stress of heart failure and signal the brain to...
alter volume regulation and autonomic function. Interestingly, the cardiovascular regions of forebrain that sense and respond to circulating peptides (19, 81, 110) also process the signals originating in cardiovascular afferent nerves (88, 107, 162) and are capable of modulating cardiovascular reflexes (11).

This brief review summarizes recent and emerging observations from our laboratory that emphasize the potential importance of humoral heart-brain signaling in the pathogenesis of heart failure. Previous reviews have dealt extensively with other aspects of autonomic dysfunction in heart failure (55, 113, 120), including the altered function of cardiovascular sensory afferents (191) and altered function of critical forebrain mechanisms, particularly within the paraventricular nucleus of hypothalamus (PVN) (122).

THE NEUROHUMORAL MILIEU OF HEART FAILURE

It is useful to consider the neurohumoral manifestations of heart failure (86) in terms of their peripheral vs. central origins. In the periphery, after myocardial infarction (MI), a number of vasoactive and neuroactive humoral factors are released (55). Among these are ANG II and aldosterone (Aldo), products of the renin-angiotensin-aldosterone (RAAS) system response to a state of reduced tissue perfusion, and the pro-inflammatory cytokines, products of immune system activation in response to myocardial injury (65). These two systems are the principal focus of this review. Both ANG II and the cytokines act peripherally to induce effects that may be beneficial (52) in the short-term but are ultimately detrimental as myocardial injury progresses to heart failure. Countering these influences are the prostaglandins PGE_2 and PGI_2, whose release may be facilitated by the combined action (4) of ANG II and the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α), and the atrial natriuretic peptides, which generally oppose the adverse effects of the RAAS (26) in heart failure.

Among neurohumoral responses in heart failure that clearly require the involvement of CNS neurons are increased thirst and sodium appetite (82), release of adrenocorticotropic hormone with consequent increase in circulating corticosterone (25), release of AVP (104) with accompanying vasoconstriction (105, 134), water retention (23), and hyponatremia (87), and augmented sympathetic nerve activity (91, 191) with associated increases in circulating norepinephrine (49). Increased sympathetic drive in heart failure is strongly associated with ventricular remodeling (17, 53) and myocardial depression (17), cardiac arrhythmias (159), and vasoconstriction (53), and is an adverse prognostic indicator (49).

The heart failure syndrome is characterized by a dynamic interplay among these centrally and peripherally driven neurohumoral responses. For example, the responses that can be attributed to activation of cardiovascular and autonomic centers of the brain are stimulated by peptides released from peripheral tissues and by altered sensory inputs from the cardiovascular system—all consequences of impaired left ventricular function. In this regard, the central sympathetic drive and the peripheral RAAS appear to be locked into a feedforward relationship—blood-borne ANG II acts on AT_1 receptors in the forebrain to increase sympathetic nerve activity, which in turn acts on the kidneys to stimulate the renin release, the rate-limiting step in the production of more ANG II. Interestingly, central manipulations of AT_1 receptors, or of brain ouabain-like activity, which also contributes to augmented sympathetic drive in heart failure (92), inhibit the progression of left ventricular dysfunction after MI (93). Presuming sympathetic mediation of this effect, the detrimental effects of sympathetic stimulation on left ventricular function are well described (17). Thus, whereas augmented RAAS in heart failure activity has direct detrimental effects on left ventricular function (36, 139, 168, 179), it is clear from this study (93) that heart-brain signaling via neurohumoral mechanisms is also an important determinant of left ventricular remodeling after ischemic myocardial injury. A similar relationship between the centrally mediated autonomic influences of circulating ANG II and the progression of heart failure has been suggested in the rapid pacing model (97). A hypothesis to be tested is that in ischemia-induced heart failure blood-borne cytokines amplify the effects of the RAAS on sympathetic drive, compounding this compromising interaction between heart and brain.

THE HYPOTHALAMUS AND PVN IN HEART FAILURE

The particular constellation of centrally driven autonomic abnormalities that define end-stage heart failure, augmented sympathetic drive in the face of vasoconstriction, salt, and water retention in the presence of volume overload, immediately suggests dysfunction of the forebrain neurons that regulate these systems under normal conditions. In a pioneering study focusing on the role of the forebrain in heart failure, Patel and colleagues (124) demonstrated that metabolic activity was increased in the parvicellular and magnocellular regions of the PVN in rats with ischemia-induced heart failure. More recently, Vahid-Ansari and Leenen (167) demonstrated that Fra-like immunoreactivity, an indicator of long-term neuronal activation, was increased in these same regions in rats with a large MI. Other studies (41, 78, 79, 145, 181, 185) demonstrated that manipulations within the forebrain region affect the regulation of sympathetic drive in the rat model of ischemic heart failure.

The anatomy and relevant physiological functions of the hypothalamus and PVN under normal conditions (19, 82, 111, 149, 163) and the potential involvement of this region in the pathogenesis of heart failure (121–123) have been reviewed in detail by others. Particularly pertinent to the heart failure syndrome are those PVN neurons that produce and release AVP and CRF (146) and those that project to the principal centers of sympathetic drive, the rostral ventrolateral medulla (RVLM) and the intermediolateral cell column (IML) of
the spinal cord (148). PVN neurons receive and integrate ascending signals from the hindbrain regions related to pressure and volume within the cardiovascular system (107) and signals from forebrain regions including the circumventricular organs of the lamina terminalis, which lack a blood-brain barrier and thus sense the presence of blood-borne neuroactive peptides (108). Figure 1 illustrates this concept, showing that the discharge rate of a single PVN neuron is increased by blood-borne ANG I or ANG II administered into the ipsilateral carotid artery (ICA) but also by a reduction in arterial pressure induced by intravenous sodium nitroprusside. A fall in arterial pressure and an increase in circulating angiotensin in response to a fall in arterial pressure would elicit the same excitatory response from this neuron. In this instance, the angiotensin affects the neuron secondarily, via an influence on neurons of the circumventricular organs of the lamina terminalis. However, angiotensin can also be produced within the blood-brain barrier (51) to activate angiotensin type-1 (AT1) receptors on PVN neurons (33, 117).

In normal rats, the PVN and related forebrain nuclei play a prominent role in thirst, sodium appetite, and humoral release (19). The role of the PVN in driving the sympathetic nervous system, however, is less clear. In the anesthetized rat, for example, electrical stimulation of the PVN elicits only a small pressor response (130). Similarly, the cardiovascular response of normal rats to activation of the forebrain region with angiotensin is small (8, 173) and is restrained by baroreceptor input (Fig. 2). Normally, the PVN is under the potent inhibitory influence of GABA and nitric oxide, as demonstrated by the striking increases in sympathetic drive that can be elicited by local injection of bicuculline or inhibitors of nitric oxide synthase (182, 183). In certain disease conditions, however, heightened sympathetic drive emanating from the PVN may become an important pathophysiological determinant. PVN lesions in the young spontaneously hypertensive rat, for example, inhibit the development of hypertension and augmented sympathetic drive (164). The augmented humoral drive and diminished baroreceptor influence favor a prominent pathophysiological role for the PVN in heart failure as well.

**MI AND PROGRESSION TO HEART FAILURE IN THE RAT**

To further define the mechanisms activating the forebrain and PVN in heart failure, our laboratory has used a multifaceted approach, combining venous sampling of circulating peptides, metabolic cage measurements of salt and water consumption and excretion, and electrophysiological recording from central neurons and from sympathetic nerves in rats with a large MI produced by ligation of the left anterior descending coronary artery and confirmed by echocardiography. All studies were performed in accordance with the “Guiding principles for research involving animals and human beings” (1a).

Animals with ischemia-induced heart failure already have significantly reduced left ventricular systolic function and an enlarged left ventricle when evaluated by echocardiography within 24 h after coronary ligation (62). Serial echocardiographic measurements demonstrate that the injured myocardium thins and the left ventricle dilates further over the ensuing 6 wk, but ejection fraction (0.36, vs. 0.82 in sham-operated controls, 2–3 wk post-MI) remains about the same (63). These heart failure rats have increased levels of

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**Fig. 1. Neural and humoral modulation of neurons in paraventricular nucleus of hypothalamus (PVN).** Single-unit recordings of PVN neuronal activity (discharge rate, spikes/s) and arterial pressure (AP, mmHg) taken from a normal rat. Top: unit activity increases in response to intracarotid artery (ICA) administration of ANG II (left) and ANG I (right). Both elicit an increase in AP. Response to ANG I implies conversion of ANG I to ANG II in forebrain to activate angiotensin type 1 receptors. Bottom: unit activity is unchanged by an increase in AP induced by intravenous phenylephrine (PE) but increases in response to lowering AP with intravenous sodium nitroprusside (SNP). The majority of PVN neurons tested demonstrated increased activity in response to a hypotensive challenge. [Borrowed with permission (186).]

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plasma renin activity, AVP, and atrial natriuretic factor (63), and of TNF-α (61) (Fig. 3). They consume more sodium than sham-operated control rats, and their urinary excretion of sodium and water is reduced (63).

In heart failure rats monitored continuously by telemetry over a 6-wk period, heart rates (HR) were higher and blood pressures lower than sham-operated controls (Fig. 4). Sympathetic nerve activity in conscious heart failure rats is increased, with a characteristic pattern of unsuppressed yet still pulse-related bursting, suggesting some degree of continued baroreceptor modulation. As shown in Fig. 5, however, the pulse-triggered average of sympathetic discharge is higher in the heart failure rats. Baroreceptor regulation of renal sympathetic nerve activity (RSNA) is blunted. Studied 1 wk after coronary ligation, they exhibit signs of psychological depression (69). Consistent with other studies using this model, left ventricular end-diastolic pressure is elevated when checked terminally. At post-mortem exam, 6–8 wk after coronary ligation, heart weight-to-body weight and lung weight-to-body weight ratios are increased and pleural and/or ascitic fluid is sometimes present. Thus rats with ischemia-induced heart failure express many features typical of human heart failure.

**TESTS OF THE FOREBRAIN HYPOTHESIS**

Using this rat model of ischemia-induced heart failure, we have performed both acute and chronic interventions to address specific questions regarding the contribution of the forebrain to the progression to heart failure after MI.

**How important is forebrain activation to the course of heart failure after MI?**

There is no question that the forebrain is a point of access for the variety of neuroactive substances, including ANG II, endothelin, atrial natriuretic peptides, and cytokines, that are produced...
Second, the expected increase in plasma renin activity did not occur in the AV3V-lesioned MI rats. These findings clearly implicate the forebrain as an active participant in the progression of heart failure and further suggest that the renin response to renal underperfusion after MI may be largely dependent on sympathetic efferent regulation emanating from the forebrain. There is some precedent for that suggestion in previous work demonstrating that electrical stimulation of PVN can increase renin release from the kidney (129) and facilitate the renin response to other usual stimuli (128). But perhaps most important was a third finding, the survival of the AV3V-lesioned MI rats was compromised to the extent that most had died 3 wk after MI, in contrast to MI rats with sham-AV3V lesion and AV3V-lesioned rats with sham MI (Fig. 6).

Thus the AV3V lesion identified the forebrain as important not only to the centrally mediated (e.g., thirst, sodium appetite) mechanisms in heart failure but to remote peripheral manifestations (e.g., renal sodium and water handling, renin release) as well. Furthermore, forebrain mechanisms appear to confer a survival benefit in heart failure that cannot be ascribed simply to the ability to muster a stress response. Work by others has shown that AV3V-lesioned rats have elevated plasma corticosterone levels and exaggerated corticosterone responses to volume depletion (12) and that CRF-producing neurons PVN can be activated by circulating cytokines despite knife cut lesions in this same general region (46). Interestingly, because plasma renin activity did not rise after MI in the AV3V-lesioned rats, this study did not actually address the contribution of the peripheral RAAS as a factor activating the forebrain in heart failure.

**Does excessive activity of the RAAS drive forebrain mechanisms in heart failure?** ANG II and Aldo, active products of the RAAS, can both act on receptors in the forebrain to induce changes in volume regulation (82) and sympathetic drive (67, 90). In heart failure, the circulating levels of these peptides are increased. Both peptides can also be produced within the blood-brain barrier (22, 66). Furthermore, Aldo increases the binding of ANG II to AT1 receptors in the subfornical organ and the PVN (35) and also increases mRNA for vasopressin in PVN and vasopressin release (144). In another context (73), Aldo has been shown to promote the activity of angiotensin converting enzyme (ACE), which produces ANG II from its precursor ANG I. ACE is present in the forebrain and is particularly abundant in the circumventricular organs of the forebrain (140, 143). Thus it is possible that Aldo may amplify the influences of circulating and intrinsically produced ANG II. Whereas most of these potential interactions have yet to be tested in the brain in heart failure, there is evidence for increased AT1 receptors in the forebrain of rats with high-output heart failure (177).

We examined the influences of the RAAS on forebrain neurons in rats with chronic heart failure (186). Single-unit recordings were made from PVN neurons in anesthetized rats 4–6 wk after MI. Heart failure was documented by echocardiography. Drugs were ad-
ministered by the intracarotid (ICA) route, directed centrally, an approach that has been shown to preferentially influence the ipsilateral forebrain and to spare the hindbrain (75).

The activity of PVN neurons was on average increased in rats with heart failure, although the discharge rate of some neurons remained within the range of normal (Fig. 7). Neurons with high discharge frequencies were tested for the effects of selectively blocking several components of the RAAS. The effects of the AT1 receptor blocker losartan, the ACE inhibitor captopril, and the mineralocorticoid (MC) receptor antagonist spironolactone were tested. Both losartan and captopril substantially and transiently reduced the discharge rate of PVN neurons and arterial pressure (Fig. 8). Spironolactone also reduced the discharge rate of PVN neurons but with a longer latency and without affecting arterial pressure.

Several new insights emerged from these studies. First, as predicted by previous work (124), neuronal activity in the PVN is generally (but not uniformly) increased in rats with ischemia-induced heart failure. The specific types of cells that have augmented activity, e.g., sympathetic premotor vs. neurosecretory, remain to be determined. Second, the RAAS, whether...
intrinsic or circulating, contributes importantly to this increased activity. Third, the captopril data indicate that intrinsic ACE activity in the forebrain is increased in the heart failure rats. In theory, because increased ANG II can upregulate AT<sub>1</sub> receptors (175), the losartan data and the captopril data might both be explained by a common mechanism, augmented CNS production of ANG II by ACE in heart failure, perhaps facilitated by Aldo, rather than an independent increase in both components of central RAAS. This hypothesis remains to be tested. Finally, despite a chronic high discharge rate in heart failure, PVN neurons remain responsive to acute manipulations of the RAAS. This latter point has important implications for the clinical treatment of heart failure, suggesting that acute interventions can have substantial impact on central neural mechanisms despite the chronic nature of the heart failure syndrome.

Will chronic manipulation of the RAAS at the forebrain level alter the course of heart failure after MI? In another set of experiments (62), we examined the effect of a selective intervention at the RAAS at the CNS level. At the time this study was designed there was increasing interest in the role of aldosterone as an untreated element in heart failure (125, 157). The recently published RALES trial (127) demonstrated that the addition of a small dose of the MC receptor antagonist spironolactone to the medical regimen of patients already optimally treated for heart failure resulted in substantial reductions in morbidity and mortality. MC receptors have well-known effects in brain to increase sodium appetite (34), ANG II binding in subfornical organ and PVN (35), vasopressin production and release into the circulation (144), and sympathetic drive (67). However, none of these central influences had been directly examined in the heart failure setting. We therefore elected to test the effect of chronic central administration of spironolactone on the clinical treatment of heart failure and to assign them to treatment groups. MI and sham-MI rats were assigned to treatment with a chronic infusion of spironolactone or its ethanol vehicle administered either intracerebroventricularly or intraperitoneally. The dose chosen for intracerebroventricular administration was known to have CNS effects (176), and the intent of the identical intraperitoneal dose was to control for potential effects of leakage from the CNS.

Central MC receptor blockade produced the expected behavioral effect of reducing salt intake in the heart failure rats. Surprisingly, however, within the first week of treatment urinary sodium and water excretion had normalized in the MI rats treated with intracerebroventricular spironolactone, whereas these variables remained abnormally low in the MI rats treated with intraperitoneal spironolactone. However, 2 wk into the protocol, rats receiving intraperitoneal spironolactone also experienced normalization of sodium appetite and renal handling of sodium and water. After 4 wk of treatment by either route, the spironolactone-treated MI rats had a reduction in sympathetic discharge (Fig. 9) and some, but not complete, improvement in baroreflex function. The impact of spironolactone treatment on survival could not be evaluated because rats were euthanized at the conclusion of the study to obtain
anatomical evidence of myocardial injury and heart failure. However, at the 2-wk time point, at which most AV3V-lesioned rats from the above study were dying post-MI, the spironolactone-treated rats appeared to be in satisfactory condition. In a follow-up study (60), we found that a reduction in sympathetic drive occurs as early as 2 wk after starting central spironolactone treatment of MI rats, an effect not seen in the MI rats treated with peripheral spironolactone. Thus, although in theory amelioration of the baroreflex effects of high circulating aldosterone (170) may have contributed to the reduced sympathetic drive and HR in the rats treated with intraperitoneal spironolactone, the results of our studies indicate that spironolactone acts centrally on MC receptors to reduce sympathetic drive in heart failure. This mechanism may account at least in part for the beneficial effect of spironolactone in the clinical setting. In our studies, the intraperitoneal dose of spironolactone was intentionally low to allow us to identify a CNS effect; at higher doses, one might anticipate an early centrally mediated effect of the peripherally administered drug as well.

THE CYTOKINE CONNECTION

In a retrospective analysis of humoral variables from this chronic spironolactone study (62), a surprising discovery was made: the circulating levels of TNF-α were normal in the MI rats treated with central infusion of spironolactone. Vehicle-treated MI rats had the anticipated increase in TNF-α (Fig. 10). Whether the brain produces less TNF-α or signals peripheral tissues to reduce cytokine production remains to be determined. However, the observation suggests a previously unrecognized central link between the immune system and the RAAS in heart failure and yet another reason why MC receptor blockade might be beneficial in heart failure.

The immune system is activated by injury or inflammation. Both MI (65) and heart failure (151) are associated with immune system activation. In the heart...
failure and MI literature, the most studied of the proinflammatory cytokines are TNF-α, interleukin-6, and interleukin-1β (6, 38, 39, 84, 118, 131). In our rat model (61), blood-borne TNF-α increases as early as 30 min after coronary artery ligation. “Resident” monocytes and macrophages within the heart (64), and myocytes themselves (32), are likely sources of circulating proinflammatory cytokines early after MI (112). However, because one of the effects of the proinflammatory cytokines is to promote further cytokine production, the sources of circulating cytokines in established heart failure are likely ubiquitous (10).

The persistence of proinflammatory cytokines in the circulation has numerous potential deleterious peripheral effects (10, 112), including depression of myocardial function (16), activation of reactive oxygen species (32), and stimulation of the renin-angiotensin system by impairing feedback regulation by circulating ANG II (3). The cytokines also act on the CNS (77, 135, 166). Although too large to readily cross the blood-brain barrier, they nevertheless activate the hypothalamic-pituitary-adrenal (HPA) axis (135) to augment sympathetic drive (116, 141) and increase the release of vasopressin and ACTH (27, 43, 106, 166), all components of a feedback inhibitory mechanism that restrains the peripheral inflammatory response. In a series of functional anatomical studies, Ericsson and colleagues (45, 46) provided evidence that acutely administered IL-1β elicits these responses indirectly by activating its receptors on endothelial cells in cerebral circulation that in turn release PGE₂. PGE₂ diffuses across the blood-brain barrier and appears to preferentially activate receptors on neurons in the ventrolateral medulla (45). These investigators further demonstrated that an ascending pathway from the ventrolateral medulla is a critical element of the PVN response to systemically administered IL-1β (46) and that stimulation of C1 catecholaminergic neurons in RVLM with PGE₂ provides excitatory input to PVN, simulating the response to intravenous cytokine administration (45). Subsequent studies have supported this general concept (116) but have further suggested that PGE₂ might activate sympathetic drive directly at the forebrain level (2), perhaps even via prostaglandin synthesis inside the blood-brain barrier (102).

This model of immune activation of the forebrain is particularly interesting when considered in the context of heart failure. In heart failure, cytokine production persists (38) despite this combined HPA and sympathetic feedback pathway, and the pro-inflammatory cytokines act on the same general classes of neurons, CRF, AVP, and presympathetic, that mediate the central effects of the RAAS. Moreover, PGE₂ production is increased generally in heart failure, in which its vasodilator properties counterbalance the vasoconstrictor effects (44) of such peptides as ANG II, vasopressin, and endothelin.

Fig. 11. A model for cytokine activation of the central nervous system in HF after MI, based on work cited in text. Injured heart itself is a site of early cytokine production, recruiting other cytokine-producing organs. Blood-borne cytokines activate their receptors in blood vessels at the blood-brain barrier, stimulating the production of prostaglandins (PGE₂) that can cross blood-brain barrier (BBB). A principal target is catecholaminergic neurons (CA) in the rostral ventrolateral medulla that project to PVN to activate neurons containing CRF and AVP and presympathetic neurons. CRF neurons regulate release of ACTH and AVP into the circulation, but some of these neurons also project to brain stem and spinal cord where they may contribute to sympathetic activation. The outcome of cytokine activation of PVN is an increase in circulating corticosterone and AVP and an increase in sympathetic drive, all feeding back to inhibit the peripheral immune system. In HF, however, cytokine production persists despite these feedback mechanisms. SNA, sympathetic drive; IML, intermediolateral cell column of the spinal cord.
This remarkable convergence of immune system mediators and RAAS mediators, seemingly affecting the same general populations of neurons in the forebrain, led us to test several elements of the proposed mechanism (Fig. 11) of cytokine-induced HPA axis activation, but in the context of cardiovascular regulation. ICA TNF-α increases RSNA, mean arterial pressure (MAP), HR, and the discharge rate of anesthetized RVLM neurons in PVN rats (187). The cardiovascular and sympathetic responses to TNF-α were not different in rats that had undergone bilateral cervical vagotomy 1 h before testing, confirming that the acute cardiovascular responses to blood-borne TNF-α are not dependent upon vagal afferent activation (188). We then compared the effects of intravenous TNF-α on RSNA, MAP, and HR in intact rats and rats that had undergone a mid-collicular decerebration 1 h before study. The decerebrate rats had no response to TNF-α, suggesting the involvement of higher centers, but a significant increase in the baseline values rendered these data inconclusive (188).

We subsequently examined the effects of the putative diffusible cytokine mediator PGE2 on sympathetic nerve discharge, arterial pressure, and HR, and simultaneously recorded PVN or RVLM neuronal activity (188). PGE2 administered intracerebroventriculally increased the activity of PVN neurons and all three measures of sympathetic drive; PGE2 microinjected into PVN increased the activity of RVLM neurons and the indexes of sympathetic drive. These studies suggest that if PGE2 is produced in the forebrain region during cytokine stimulation, it may directly activate sympatho-excitatory PVN neurons. Finally, the cyclooxygenase inhibitor ketorolac, administered intracerebroventricularly, blocked the increases in PVN neuronal discharge and RSNA and the pressor response to ICA TNF-α (188). These results strongly support the general hypothesis that PGE2 is a critical mediator of central influences of TNF-α on sympathetic drive, but also suggest that the cardiovascular and autonomic responses to TNF-α may ultimately be dependent on prostaglandin production by cyclooxygenase within the CNS rather than in perivascular cells of the blood-brain barrier (45, 135). A similar mechanism has also been proposed for activation of splenic nerve activity by peripheral endotoxin (102), a stimulus to cytokine production. We have not yet tested this hypothesis with antagonists for PGE2 in the key CNS sites (RVLM and PVN).

Extrapolating these concepts and findings to the heart failure setting, one might speculate that cytokine signaling of the HPA, which under normal circumstances serves to regulate the immune system, targets a population of PVN neurons that are already strongly driven in heart failure by excessive activity of the RAAS. Are these two systems redundant or facilitatory? In preliminary studies (unpublished data) the acute administration of entanercept to rats with heart failure appears to decrease PVN neuronal activity, presumably by reducing circulating TNF-α. This observation suggests that circulating TNF-α affects PVN neurons independently of RAAS. Further studies will be required to address the relative contributions of cytokines and RAAS to the altered central regulation of fluid volume and sympathetic drive in heart failure.

It is important to note that our preliminary results (187, 188) regarding the central effects of TNF-α and PGE2, and much of the data cited from the pertinent literature regarding cytokine mechanisms and effects (2, 45, 46, 101, 102), are derived from acute immune challenges or interventions. In the chronic, established heart failure setting, other mechanisms may be operative. Thus, although the passage of cytokines is restricted by the blood-brain barrier, active transport mechanisms exist (7) that may facilitate their entry under conditions such as heart failure that are characterized by chronically elevated circulating cytokine levels. Signaling via vagal afferents (103) may play a more prominent role. The brain itself is capable of producing cytokines (119), and neuronal content of cytokines is increased in certain chronic disease states (138). Interestingly, mice treated with continuous infusion of high dose PGE2, simulating the high levels in heart failure, demonstrate increased brain cytokine content (169). In our preparation, using immunohistochemistry and real time RT-PCR, mRNA for TNF-α is increased in hypothalamic neurons as early as 60 min after MI (56).

The potential production of proinflammatory cytokines in the brain itself raises interesting untested possibilities for interactions between the RAAS and cytokines. Does TNF-α promote renin production in the brain as it does in the kidney (3), stimulating brain RAAS? Does TNF-α upregulate the message for AT1 receptors in the brain after MI, as it does in heart (71)? Does TNF-α stimulate prostaglandin synthesis within the blood-brain barrier, providing an excitatory input to forebrain neurons? Both TNF-α (32) and RAAS (68) can stimulate reactive oxygen species, which may also drive sympathetic activity (189). Does the presence of both in forebrain contribute to the increased sympathetic drive in heart failure? If TNF-α production increases in the forebrain early after MI in rats (56), and brain is a potential source of circulating TNF-α (132), to what extent is brain a source of the high circulating levels of TNF-α in heart failure vs. a command center signaling peripheral tissues to produce cytokines? These and related questions are fertile ground for future studies of the contribution of pro-inflammatory cytokines to the progression of heart failure.

**SYMPATHETIC DRIVE IN HEART FAILURE: A HYPOTHETICAL CONSTRUCT**

The PVN is clearly emerging as a pivotal site in the forebrain that responds to the peripheral signals of homeostatic imbalance in a manner that is at once both essential to survival and detrimental if perpetuated over time. Some of the peripheral signals that may impact the function of this region of the brain in heart failure are illustrated in Fig. 12A, in the context of sympathetic regulation. PVN neurons directly innervate preganglionic sympathetic neurons in the IMl, as
well as presympathetic neurons in the RVLM and neurons in the nucleus of the solitary tract (NTS), the site of first termination for cardiovascular afferent nerve fibers (31, 74, 96, 158, 163).

We know that cardiovascular afferent systems are altered in heart failure (192). The activity of sympatho-inhibitory systems, such as the high-pressure arterial baroreceptors (190) and low-pressure cardiac mechanoreceptors (192), is reduced, whereas the activity of sympato-excitative systems, such as arterial chemoreceptors (161) and cardiac sympathetic afferent fibers (171), is increased. The central processing of these afferent signals is also altered (99, 100). The cardiovascular afferent signals entering the NTS ultimately affect the discharge of PVN neurons, via direct projections from NTS or a more circuitous route involving a synapse in the ventrolateral medulla (29, 107, 147).

For example, the majority of PVN neurons responding to ICA ANG II also respond to changes in arterial pressure (186), and baroreceptor regulation of vasopressin release is a well recognized phenomenon (165). Thus the increased activity of PVN neurons in heart failure likely reflects the compromised state of cardiovascular afferent systems, whether at the sensory ending, in the afferent fiber, or in the hindbrain processing of the afferent signal.

The excessive activity of the peripheral RAAS in heart failure may influence PVN neurons indirectly, via actions of circulating ANG II on neurons in the circumventricular organs (110) of the forebrain. With chronic elevation of ANG II, one might also anticipate an influence from area postrema, a circumventricular organ in the medulla (54). In addition, there is suggestive evidence that the activity of the intrinsic brain RAAS may be upregulated in heart failure (177). As mentioned above, Aldo may facilitate the forebrain actions of the peripheral or intrinsic RAAS (35).

Finally, as illustrated in Fig. 12B, immune system activation may influence PVN neurons indirectly via the production prostaglandin mediators (45, 136), directly via transport of cytokines across blood-brain barrier (7), or by as yet poorly understood effects of cytokine production within the blood-brain barrier itself (56, 119, 169). In our studies (188), vagal afferent activation (103) did not seem to affect PVN or sympathetic responses to the acute administration of TNF-α, but a role for this afferent pathway in established heart failure, in which cytokines are chronically elevated, cannot be excluded.

Multiple interactions among these three regulatory systems are possible within PVN. For example, the connections ascending from NTS and ventrolateral medulla that convey afferent signals generated by cardiovascular afferent inputs (147) are predominantly catecholaminergic. The cytokine influence on PVN

![Fig. 12. Extrinsic factors affecting regulation of SNA by the PVN in heart failure. A: Descending pathways from PVN are shown in double lines. PVN neurons project monosynaptically to rostral ventrolateral medulla (VLM), the nuclei of the solitary tracts (NTS), and the IML, all of which may affect SNA. In HF, peripheral sensory receptors that project centrally to modulate sympathetic drive are altered, with reduced arterial baroreceptor restraint of SNA and increased arterial chemoreceptor stimulation of SNA. These signals (dashed lines) initially impinge on neurons in the NTS and from there are relayed rostrally either directly or indirectly (e.g., via VLM) to affect the activity of PVN neurons. Blood-borne products of the renin-angiotensin-aldosterone system (RAAS) may activate the forebrain directly (e.g., aldosterone) or via effects on circumventricular organs, and intrinsic components of RAAS may be stimulated to generate these peptides locally within the forebrain. Influences of the RAAS are illustrated as squiggly lines. B: Putative influences of the cytokines in HF are shown superimposed on the schema A. There are several mechanisms, shown as dotted lines, by which cytokines might activate PVN neurons driving sympathetic activity. By binding to receptors on vascular endothelium or other elements of the BBB, circulating cytokines stimulate the production of PGE₂, which diffuses readily across BBB. With respect to acute activation of the hypothalamic-pituitary-adrenal (HPA) axis, it has been suggested that PGE₂ preferentially stimulates catecholaminergic (CA) neurons in the RVLM that then ascend to activate neurons in the PVN. In HF, in which cytokine levels are chronically elevated, other mechanisms may come into play. These include peripheral activation of vagal afferent fibers, activation of circumventricular neurons with secondary projections to PVN, passage of cytokine across BBB via active transport mechanism, and production of cytokines by neurons and glial cells within the BBB. The mechanism for cytokine activation of SNA, their interactions with altered peripheral afferent systems and RAAS, and their contribution to the augmented SNA in heart failure are still poorly understood.](http://ajpregu.physiology.org/Content/Full/284/2/R269)
neurons is also mediated at least in part by catecholaminergic neurons ascending from RVLM (46). A cytokine-mediated increase in norepinephrine release into PVN has also been demonstrated after peripheral injection of endotoxin (58). ANG II has a pronounced effect on norepinephrine release within the PVN (156). All three systems, cytokines, cardiovascular afferents, ANG II, influence the activity of CRF neurons, AVP neurons, and presympathetic neurons in PVN, which are modulated by catecholaminergic inputs (20, 27, 30, 70, 76, 80). Moreover, norepinephrine is critical to the regulation of autonomic functions by this region of the brain (13, 24). For example, catecholamine depletion in ventral lamina terminalis blocks drinking and pressor effects of ANG II, via effects on adrenergic neurons (14). Thus a parsimonious unifying hypothesis to explain the coordinated excesses of neurohumoral drive emanating from this region of the brain in heart failure might be intense catecholaminergic stimulation of PVN neurons, perhaps overwhelming local regulatory systems (see below). In rats with ischemia-induced heart failure, an in vivo microdialysis study (9) demonstrated a striking increase in norepinephrine release into PVN compared with sham-operated control animals. In humans with heart failure, excessive catecholamine turnover in the brain correlates with augmented drive (89).

Finally, although this review has focused on the convergence of neural and humoral signals that might drive the activity of PVN neurons, it is important to remember that altered neurotransmitter mechanisms within the PVN itself contribute to altered PVN neuronal function and sympathetic drive in heart failure. GABA and nitric oxide clearly play an important role in regulating PVN neurons in normal rats (183). The potential contribution of the altered function of these mechanisms within PVN to the augmented sympathetic drive in heart failure has been extensively examined and reviewed by Patel and colleagues (122). The influence of inhibitory mechanisms within PVN is substantially diminished in rats with heart failure (180, 181, 184), and the influence of excitatory mediators is increased (94). In part, these changes may reflect altered neural inputs to PVN. For example, GABA is involved in the baroreceptor modulation of neurosecretory PVN neurons (85); a reduction in baroreceptor function in heart failure might well result in a reduction of GABA levels in PVN.

**TRANSLATIONAL ASPECTS**

Despite recent advances in the treatment and the primary prevention of heart failure (1, 115, 168, 178), the long-term prognosis for patients who present with this diagnosis remains dismal and the economic burden to the health care system is huge (47, 133). In this perspective, a consideration of the role of the brain may be critically important in the development of effective therapeutic strategies.

ACE inhibitors and diuretics are first-line therapy for patients with heart failure. This same drug combination has been used for years by physiologists to stimulate thirst in normal rats by increasing circulating levels of ANG I, which is converted to ANG II in the forebrain to stimulate AT$_1$ receptors (82). The circumventricular organs of the forebrain contain higher concentrations of ACE than any peripheral tissue (140, 143), including the lungs, which are the principal site...
for conversion of circulating ANG I to ANG II. Experimentally, lower dose ACE inhibitor has been shown to stimulate forebrain neurons, an effect blocked by higher doses (109). Interestingly, in that study, pre-treatment with an AT1 receptor blocker prevented the low dose effect. In our experiments, lower doses of systemically administered ACE inhibitor reduced arterial pressure, a peripheral effect of diminished ANG II-mediated vasconstriction and/or increased bradykinin-mediated vasodilation, but actually increased PVN neuronal activity (Fig. 13). Because clinical dosing of ACE inhibitor is frequently empiric, and if monitored at all is primarily directed toward the clinical endpoint of reducing systemic vascular resistance, it is likely that the doses used are sufficient to increase circulating ANG I but insufficient to block the conversion of ANG I to ANG II by ACE in the CNS. Thus it is reasonable to hypothesize that an unrecognized source of thirst, sodium appetite, and increased sympathetic drive persists despite seemingly appropriate treatment. One might also hypothesize that the concomitant use of AT1 receptor blockers would ameliorate these potential untoward CNS effects of ACE inhibition. These hypotheses are amenable to clinical testing.

The addition of an MC receptor antagonist to a standard heart failure regimen has recently been shown to have a dramatic impact on morbidity and mortality (127). This result could not be attributed to a diuretic effect. Aldo is known to “escape,” or at least to be inadequately suppressed, in a substantial number of patients treated with ACE inhibitor (125, 159) and has been shown to have deleterious effects on the heart and vasculature (172) and to impair the baroreflex (170). Aldo also has CNS effects, described above, to augment sympathetic drive (67) and vasopressin release (144) and may facilitate the central influences of ANG II (35, 160, 175). We have found that the MC receptor antagonist spironolactone, acting centrally, decreases renal sympathetic activity (62), improves renal handling of sodium and water (62), and reduces circulating levels of TNF-α (61) in rats with heart failure. The hypothesis that central MC receptors play a role in regulating the production of TNF-α is strengthened by the finding that deoxycorticosterone, a precursor of Aldo, induces sodium appetite and an increase in circulating levels of TNF-α (57), an effect that is blocked by central administration of spironolactone (57). Whether spironolactone, or the more selective MC receptor antagonist eplerenone (37), which is currently undergoing clinical testing (126), has similar beneficial effects in humans remains to be determined. This, too, is a readily testable hypothesis.

New strategies directed toward treatment of the central influences of RAAS patients with heart failure will require a reconsideration of pharmacological properties of commonly available drugs and perhaps development of drugs that specifically target the CNS. Although currently used ACE inhibitors, AT1 receptor blockers and MC receptor antagonists may act upon the CNS, either by crossing blood-brain barrier (95, 150, 174) or by acting upon the circumventricular organs that lack a blood-brain barrier (50, 137, 140, 142), their design and clinical usage target peripheral endpoints. Ideally, it might be possible to continue treating the adverse peripheral consequences of RAAS, e.g., vasoconstriction, cardiac and vascular remodeling, while increasing the ability of these agents to penetrate brain regions whose intrinsic RAAS activity may actually be augmented by predominantly peripheral ACE inhibition in heart failure. The forebrain circumventricular organs, rich in ACE (140, 143) and AT1 receptors (50, 142) and lacking the protection of the blood-brain barrier, would appear to be easily accessible targets for therapeutic intervention.

A limited understanding of cytokine mechanisms has precluded aggressive clinical treatment of the immune system in heart failure. In fact, etanercept, a fusion protein that binds circulating TNF-α has recently been withdrawn from a major clinical trial in heart failure due to lack of efficacy (98). Etanercept has been efficacious in the treatment of rheumatoid arthritis (83), and both etanercept and infliximab, a monoclonal antibody to TNF-α, are both currently used in the treatment of inflammatory bowel disease (83), two other chronic clinical conditions characterized by increased circulating TNF-α, and have beneficial effects in a number of other inflammatory diseases (83). Considering the wide range of adverse effects of blood-borne TNF-α in heart failure, some of which have been touched upon in this review, it seems likely that these agents will eventually reach the clinical heart failure arena. Whereas blood-borne TNF-α seems an obvious target for intervention, its presence in the blood indicates excessive production of TNF-α at the cellular level. In that regard, pentoxifylline, which inhibits the production of TNF-α (5) and has been used clinically for many years to treat vascular insufficiency (114), has shown some promise in small clinical studies of heart failure (153, 154). Thalidomide also inhibits TNF-α production (48). In the context of the potential CNS effects of TNF-α, our data suggest that limiting tissue production and binding circulating cytokines might both be useful therapeutic approaches in heart failure.

Our data have also confirmed a role for prostaglandins as mediators of the cardiovascular and autonomic effects of circulating TNF-α, resembling their effects as mediators of cytokine activation of the HPA axis (45) and have demonstrated a beneficial effect of a centrally administered cyclooxygenase inhibitor on these cardiovascular endpoints. It is important to note, however, that systemic cyclooxygenase inhibition is counterproductive in severe heart failure, because it eliminates the beneficial compensatory vasodilator effects of circulating PGE2 and PGI2 (72). The demonstration that cyclooxygenase inhibition within the CNS blocks the sympatho-excitatory influences of circulating TNF-α suggests an alternative and potentially less compromising site for intervention in prostaglandin synthesis in heart failure, but the safety and effectiveness of a chronic intervention at the CNS level has not yet been tested even in experimental heart failure.
Finally, it is important to realize that the intense focus of investigators on TNF-α may have distracted attention from other cytokines that are also present and active in heart failure and that may have similar deleterious or perhaps even beneficial effects. Although TNF-α is an early responder in the cytokine cascade (28), the effect of blocking blood-borne TNF-α or inhibiting its production on the presence and impact of other cytokines in heart failure still remains to be determined.

SUMMARY

Recent experimental studies have confirmed a critical role for the forebrain in the pathogenesis of heart failure after a large MI, the most common cause of heart failure in Western societies. Peripheral systems adapting to myocardial injury and reduced cardiac output release humoral factors that enlist the forebrain to help restore volume and pressure within the cardiovascular system. Unrestrained by the usual negative feedback mechanisms, peripheral and central compensatory systems persist in a futile effort to restore homeostasis. The clinical approach to the heart failure syndrome is complicated by the fact that these compensatory mechanisms are initially supportive but are ultimately detrimental. The challenge is to develop therapeutic strategies that recognize the wisdom of adaptive mechanisms but prevent the excesses that promote clinical deterioration. A rational approach will modulate but will not eliminate these mechanisms. The forebrain may be a prime target for such interventions.

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