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Mineralocorticoid Receptors, Inflammation and Sympathetic Drive in Heart Failure

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Abstract

Appreciation for the role of aldosterone and mineralocorticoid receptors in cardiovascular disease is accelerating rapidly. Recent experimental work has unveiled a strong relationship between brain mineralocorticoid receptors and sympathetic drive, an important determinant of outcome in heart failure and hypertension. Two putative mechanisms are explored in this manuscript. First, brain mineralocorticoid receptors may influence sympathetic discharge by regulating the release of pro-inflammatory cytokines into the circulation. Blood-borne pro-inflammatory cytokines act upon receptors in the microvasculature of the brain to induce cyclooxygenase-2 activity and the production of prostaglandin E_2, which penetrates the blood-brain barrier to activate the sympathetic nervous system. Second, brain mineralocorticoid receptors may influence sympathetic drive by upregulating the activity of the brain renin-angiotensin system, resulting in NAD(P)H oxidase dependent superoxide production. A potential role for superoxide dependent mitogen-activated protein kinase signaling pathways in the regulation of sympathetic nerve activity is also considered. Other potential downstream signaling mechanisms contributing to mineralocorticoid receptor mediated sympathetic excitation are under investigation.

Introduction

The traditional view of aldosterone as a hormone acting primarily upon receptors in the kidneys and the colon to conserve sodium has undergone substantial modification in the past two decades (Connell & Davies, 2005), as evidence has emerged for its involvement in cardiac and vascular fibrosis (Weber *et al.*, 1995), central nervous system mechanisms regulating sodium appetite (De Nicola *et al.*, 1992) and sympathetic nerve activity (Francis *et al.*, 2001a), and experimental models of hypertension (Gomez-Sanchez *et al.*, 1990) and heart failure (HF) (Francis *et al.*, 2001a; Lal *et al.*, 2004). Interest in the role of aldosterone in cardiovascular diseases was heightened by the Random Aldactone Evaluation Study (RALES), a large clinical trial demonstrating that the addition of a small oral dose of the mineralocorticoid receptor (MR) antagonist spironolactone (SL) to the regimen of otherwise optimally managed patients with established heart failure dramatically reduced morbidity and mortality (Pitt *et al.*, 1999). The mechanism(s) accounting for these beneficial effects were unknown (Rousseau *et al.*, 2002).

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Activation of MR in the brain has long been associated with increased salt appetite (De Nicola *et al.*, 1992) and sympathetically mediated hypertension (Gomez-Sanchez, 1997). It is therefore reasonable to hypothesize that blocking the activation of brain MR might account, at least in part, for the salutary influences of SL in HF. That hypothesis was tested in a rat model of systolic HF induced by coronary artery ligation, to mimic coronary artery disease, a leading cause of systolic HF in humans (Writing Group *et al.*, 2009).

The rat model of systolic HF

Ischemia-induced HF in rats resembles end-stage human systolic HF (Kjaer & Hesse, 2001) in many respects (Francis *et al.*, 2001b). The left ventricular (LV) ejection fraction is reduced immediately following coronary artery ligation, to about 35% with >80% being normal for rats. Over the ensuing 4–6 weeks, LV ejection fraction does not change significantly, but LV end-diastolic pressure rises and LV volume increases to a greater extent than LV mass, increasing the stress on the LV wall and presaging end-stage HF (Francis *et al.*, 2001b). The sympathetic and renin-angiotensin systems are activated in response to the low cardiac output of the injured LV. Circulating angiotensin II (Leenen *et al.*, 1999), aldosterone (Yu *et al.*, 2008), atrial natriuretic factor (Francis *et al.*, 2001b), and pro-inflammatory cytokines (Francis *et al.*, 2004a; Kang *et al.*, 2006) are all increased. These HF rats have an increased appetite for sodium, offered as a 1.8% sodium chloride solution, and their renal excretion of sodium and water is reduced (Francis *et al.*, 2001a; Francis *et al.*, 2001b; Francis *et al.*, 2004b). There is no measurable increase in body weight, but wet lung to body weight and right ventricular to body weight ratios increase (Kang *et al.*, 2006; Kang *et al.*, 2008), indicating volume accumulation and increased pulmonary artery pressures and stress on the right heart. Occasionally these animals are found to have ascites or pleural effusions 4–6 weeks after coronary artery ligation.

Brain MR and manifestations of HF in the rat

SL or vehicle was infused continuously into the 3rd cerebral ventricle of rats with ischemia-induced HF for 4 weeks, beginning 24 hours after coronary artery ligation. HF rats treated with ICV SL had less renal sympathetic nerve activity (RSNA), improved baroreflex control of RSNA and heart rate, and normalization of the sodium consumption and renal handling of sodium and water than HF rats treated with ICV vehicle (Francis *et al.*, 2001a). The reduction in salt appetite is a behavioral response that would be predicted by the well-known effects of MR agonists to stimulate sodium ingestion (De Nicola *et al.*, 1992). The improvements in kidney function, with increased urine volume and sodium excretion, are less easily explained. However, there is evidence that inhibition of brain MR affects kidney function via the renal nerves (Rahmouni *et al.*, 1999). Thus, it seems likely that the beneficial effect of ICV SL on renal function in this study resulted from the reduction in RSNA. Of note, a systemic infusion of the same dose of SL had no effect on renal function over the first two weeks of treatment. These findings suggest that activation of brain MR contributes to the dysregulation of sympathetic drive and to sympathetically-mediated renal dysfunction in HF.

How do brain MR regulate sympathetic drive?

The mechanisms by which activation of brain MR stimulates the sympathetic nervous system in HF remain obscure. Activation of MR can elicit both genomic and non-genomic actions (Grossmann & Gekle, 2008). Our data suggest that stimulation of brain MR upregulates the activity of other central excitatory systems, thereby augmenting the excitatory neurochemical milieu in cardiovascular regions of the brain.

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Brain MR and the pro-inflammatory cytokines

One excitatory mediator that responds to manipulations of brain MR is tumor necrosis factor – alpha (TNF-α), a pro-inflammatory cytokine. Plasma levels of TNF-α are high in patients with severe HF (Dibbs *et al.*, 1999) and correlate with adverse outcome (Deswal *et al.*, 2001). Rats with ischemia-induced HF also have high circulating levels of TNF-α. However, a continuous ICV infusion of SL, initiated within 24 hours of coronary artery ligation, prevents the expected rise in plasma TNF-α levels (Figure 1) (Francis *et al.*, 2003b). Conversely, in normal rats, treatment with the MR agonist deoxycorticosterone acetate in a dose sufficient to induce sodium appetite increases plasma TNF-α levels; and this effect is prevented by ICV administration of SL (Francis *et al.*, 2003a). These two studies demonstrated the surprising finding that plasma levels of pro-inflammatory cytokines are regulated, at least in part, by brain MR.

How might the influence of brain MR on circulating cytokines affect sympathetic drive? A brief review of the literature regarding the effect of pro-inflammatory cytokines on the hypothalamic-pituitary-adrenal (HPA) axis may provide context. Blood-borne pro-inflammatory cytokines activate the HPA axis to increase circulating glucocorticoid, catecholamines and sympathetic drive (Turnbull & Rivier, 1999; Chrousos, 2000; Dunn, 2000; Rivest *et al.*, 2000). However, since the pro-inflammatory cytokines are too large to readily cross the blood-brain barrier, it is not obvious how they accomplish this. Several mechanisms have been proposed (Turnbull & Rivier, 1999; Chrousos, 2000). A leading theory is that they act upon receptors in the vasculature to induce cyclooxygenase-2 (COX-2), resulting in the production of prostaglandins that are able to cross the blood-brain barrier to activate E-prostanoid receptors on central neurons (Rivest *et al.*, 2000). In a series of experiments exploring this hypothesis in detail, Sawchenko and colleagues demonstrated that acutely injected interleukin-1 beta (IL-1β) induces COX-2 activity in perivascular macrophages lining the cerebral vasculature (Schiltz & Sawchenko, 2002, 2003), that microinjection of prostaglandin E_2 (PGE_2) into the rostral ventrolateral medulla (RVLM) activates corticotropin releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN)(Ericsson *et al.*, 1997), and that IL-1β-induced activation of CRH neurons is prevented by interrupting noradrenergic pathways ascending from the RVLM (Ericsson *et al.*, 1994). These studies strongly suggest that PGE_2 mediates the acute affects of systemically administered pro-inflammatory cytokines on the HPA axis.

We first examined this potential link between blood-borne cytokines, COX-2 and sympathetic drive further in normal rats. An acute intracarotid injection of TNF-α, directed toward the brain, elicited increases in heart rate, RSNA, arterial pressure, and neuronal excitation in both PVN and RVLM (Zhang *et al.*, 2003). All these responses were prevented in rats pretreated with ICV administration of the cyclooxygenase inhibitor ketorolac. These findings were consistent with the known sympatho-excitatory effect of ICV PGE_2 (Hoffman & Schmid, 1979; Feuerstein *et al.*, 1982), and confirmed the role of PGE_2 as the central mediator of sympathetic responses to an acutely administered cytokine challenge.

We then hypothesized that COX-2 activity and PGE_2 production by the cerebral vasculature might contribute to sympathetic excitation in HF, a setting characterized by chronic elevations of circulating cytokines. In HF rats, we found intense COX-2 staining in the microvasculature of the PVN (Kang *et al.*, 2006), subsequently localized to perivascular macrophages in the PVN (Yu *et al.*, 2007). This intense COX-2 staining was closely associated with marked activation of PVN neurons, as indicated by Fra-like activity (Kang *et al.*, 2006). Notably, HF rats treated orally with the MR antagonist eplerenone for 6 weeks had lower plasma levels of IL-1β, less COX-2 staining in the vessels penetrating the PVN and less PVN neuronal excitation (Figure 2) (Kang *et al.*, 2006). Studies using the cytokine

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synthesis inhibitor (pentoxifylline) and the recombinant human soluble tumor necrosis factor-α receptor complex (etanercept) yielded very similar results (Kang *et al.*, 2006), suggesting that the central effects of eplerenone were secondary to the reduction in blood-borne cytokines. Combined treatment with eplerenone and etanercept had no additional effect (Kang *et al.*, 2006). In addition, treatment with eplerenone, pentoxifylline, etanercept and eplerenone plus etanercept had similar effects on CSF PGE_2, a biological index of COX-2 activity and the presumed mediator of cytokine-induced sympathetic drive, as well as on plasma norepinephrine, a surrogate measure of sympathetic drive (Kang *et al.*, 2006).

Taken together, these studies suggest that one mechanism for the MR-mediated increase in sympathetic nerve activity in HF is a centrally mediated increase in circulating cytokines. How and where in the central nervous system MR agonists act to effect an increase in circulating cytokines remains to be determined.

Brain MR and the brain renin-angiotensin system

Aldosterone levels increases in brain as well as in the plasma in rats with HF (Yu *et al.*, 2008). Aldosterone of adrenal origin can cross the blood-brain barrier, though brain levels are tightly regulated (Connell & Davies, 2005), and aldosterone levels in the brain have been shown to fluctuate in response to changes in plasma levels (Gomez-Sanchez *et al.*, 2005; Yu *et al.*, 2008). In adrenalectomized rats, brain aldosterone levels are present but very low (Gomez-Sanchez *et al.*, 2005; Yu *et al.*, 2008) and increase in proportion to peripherally infused aldosterone (Yu *et al.*, 2008). However, the brain itself is also capable of producing aldosterone (Connell & Davies, 2005), so the origin of the aldosterone in the brain of HF rats remains uncertain (Yu *et al.*, 2008; Huang *et al.*, 2009).

Aldosterone has actions in the brain similar to those of angiotensin II, promoting sodium and water consumption and increasing sympathetic drive (De Nicola *et al.*, 1992; Gomez-Sanchez *et al.*, 1996; McKinley *et al.*, 1996). We hypothesized that activation of brain MR might upregulate the activity of the brain renin-angiotensin system. We tested this hypothesis in HF rats treated for 4 weeks with a continuous ICV infusion of the MR antagonist RU28318 (Yu *et al.*, 2008). Compared with sham-operated control rats, untreated HF rats had increased hypothalamic mRNA and protein for angiotensin converting enzyme and angiotensin II type 1 receptors (AT_1R), two key components of the brain renin-angiotensin system (Figure 3), consistent with previous findings from our laboratory and others (Tan *et al.*, 2004; Guggilam *et al.*, 2008; Kang *et al.*, 2008; Wei *et al.*, 2008). They also had increased hypothalamic NAD(P)H oxidase activity, as demonstrated by increased mRNA for the NAD(P)H oxidase subunits $p47^{phox}$ and $gp91^{phox}$, increased NAD(P)H oxidase dependent superoxide production, and increased intracellular superoxide in the PVN, as reported previously (Guggilam *et al.*, 2007; Kang *et al.*, 2008). Activation of the renin-angiotensin system, with downstream NAD(P)H oxidase dependent superoxide production, is closely associated with increased sympathetic drive (Zimmerman *et al.*, 2002; Gao *et al.*, 2004). These untreated HF rats had increased Fra-like activity in the PVN, signifying chronic neuronal excitation, and increased plasma norepinephrine, consistent with increased sympathetic nerve activity. All of these findings were ameliorated in the HF rats treated with ICV RU28318 (Yu *et al.*, 2008). Notably, these same manifestations were elicited in normal rats subjected to a week-long continuous ICV infusion of aldosterone, and were blocked by concomitant ICV administration of RU28318 (Zhang *et al.*, 2008). These studies support the hypothesis that activation of brain MR augments sympathetic drive, at least in part, by upregulating the activity of the brain renin-angiotensin system. An alternative explanation for the activation of NAD(P)H oxidase might be a non-genomic direct effect of aldosterone that has been demonstrated in peripheral tissues (Callera *et al.*, 2005).

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Downstream signaling mechanisms - substrates for excitatory interactions

The neurochemical milieu in cardiovascular regions of the heart failure brain is complex. The brain renin-angiotensin system is upregulated (Tan *et al.*, 2004; Liu *et al.*, 2006), the pro-inflammatory cytokines are increased (Francis *et al.*, 2004a; Kang *et al.*, 2008), and aldosterone is present in higher than normal levels (Yu *et al.*, 2008). It is likely that these excitatory mediators utilize common effector mechanisms. Thus, angiotensin II (Gao *et al.*, 2004), the pro-inflammatory cytokines (Guggilam *et al.*, 2007)and aldosterone (Yu *et al.*, 2008) all activate NAD(P)H oxidase in the brain, and all three are known to stimulate NAD(P)H oxidase dependent mitogen-activated protein kinase (MAPK) pathways – i.e, p44/42 MAPK, p38 MAPK and c-Jun N-terminal kinase (Torres & Forman, 2003). Gene products downstream from these three major MAPK pathways include AT_1R, the pro-inflammatory cytokines TNF-α, IL-1β, and COX-2. It is easy to imagine that AT_1R generated by this mechanism might bind with ambient angiotensin II, and that PGE_2 produced by COX-2 might bind with ambient E-prostanoid receptors, both ultimately resulting in increased sympathetic nerve activity. Similarly, one might anticipate a feed-forward mechanism, by which the gene products of the MAPK pathways tend to reactivate and perpetuate it, perhaps contributing to the sustained sympathetic drive characteristic of the HF syndrome.

Previously published work has demonstrated that acute inhibition of brain p44/42 MAPK activity reduces mean arterial pressure, heart rate, and renal sympathetic nerve activity in rats with established HF (Wei *et al.*, 2008), and that systemically administered angiotensin II upregulates the activity of all three MAPK pathways in the PVN and the subfornical organ in normal rats (Wei *et al.*, 2009). Preliminary data suggests that aldosterone may also utilize this pathway – a 4 hour systemic infusion of aldosterone increases expression of phosphorylated p44/42 and p38 MAPK in hypothalamus and specifically in PVN, and ICV infusion of a p44/42 MAPK inhibitor (but not a p38 MAPK inhibitor) prevents increases in heart rate, mean arterial pressure, and RSNA induced by the aldosterone infusion (Zhang *et al.*, 2009).

Summary

The mechanisms by which activation of MR induces an increase in sympathetic discharge remain obscure. The data presented here suggest several possibilities, including indirect effects mediated by pro-inflammatory cytokines and/or upregulation of the brain renin-angiotensin, and possibly even direct effects mediated by NAD(P)H oxidase dependent generation of superoxide and superoxide dependent cell-signaling pathways. Further studies are needed to elucidate the significance of these mechanisms and others that may contribute but are not yet appreciated.

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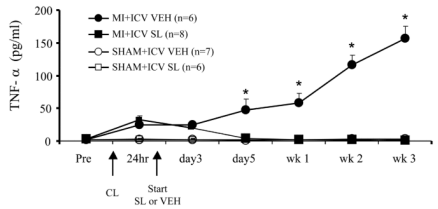

Figure 1.

Effect of central mineralocorticoid receptor blockade on plasma TNF-α levels in rats following myocardial infarction (MI). Rats underwent implantation of a cannula for chronic ICV administration of the mineralocorticoid receptor antagonist spironolactone (SL) or vehicle (VEH). Two weeks later they underwent coronary artery ligation (CL) to induce MI or a sham operation (SHAM). MI and SHAM rats received a continuous ICV infusion of SL or VEH via osmotic minipump for three weeks, beginning approximately 24 hours after coronary artery ligation and echocardiographic confirmation of left ventricular function. Jugular venous samples were collected for measurement (by ELISA) of plasma TNF-α level at the intervals indicated. * $P<0.05$, SL vs VEH in MI rats. Adapted from (Francis *et al.*, 2003b)

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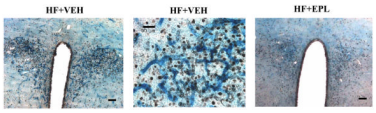

Figure 2.

Effect of chronic oral administration of the mineralocorticoid receptor antagonist eplerenone (EPL) on cyclooxygenase-2 (COX-2) expression and neuronal excitation in the paraventricular nucleus of hypothalamus (PVN) in rats with ischemia-induced heart failure (HF). Representative immunohistochemical images showing COX-2 (blue stain) and Fra-like activity (black dots) in sections taken from the PVN of rats with HF six weeks following coronary artery ligation. Left panel: coronal section showing the full expanse of the PVN in a rat with HF. Bar = 100 μm. Middle panel: a higher power view illustrating the localization of COX-2 staining to the extensive microvasculature penetrating the PVN and the proximity of COX-2 staining to chronically excited (Fra-like positive) neurons in a rat with HF. Bar = 30 μm. Right panel: coronal section showing the full expanse of the PVN in a HF rat treated orally with EPL for six weeks. Bar = 100 μm. Adapted from (Kang *et al.*, 2006)

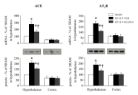

Figure 3.
Effect of central mineralocorticoid receptor blockade on components of the brain renin-angiotensin system. mRNA and protein expression of angiotensin converting enzyme (ACE, left panels) and angiotensin II type 1 receptors (AT_1R, right panels) in hypothalamus and cortex of rats with heart failure (HF) treated for 4 weeks with a continuous ICV infusion via osmotic minipump of VEH or the mineralocorticoid receptor antagonist RU28318 and of sham operated control rats (SHAM) * $P<0.05$ vs. SHAM; † $P<0.05$, HF+ICV RU28318 vs. HF+ ICV VEH. Adapted from (Yu *et al.*, 2008).

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