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## Pharmacological Treatment of Heart Failure – A View from the Brain

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### Introduction

Systolic heart failure is a feed-forward phenomenon with devastating consequences. Impaired cardiac function is the initiating event, but central nervous system mechanisms activated by persistent altered neural and humoral signals from the periphery play an important sustaining role. Animals with experimentally induced heart failure have neurochemical abnormalities in the brain that, when manipulated, profoundly affect sympathetic drive, volume regulation and cardiac remodeling – critical determinants of outcome. This brief review explores recent studies that provide a strong rationale for the development of pharmaceutical agents that target the central nervous system abnormalities in heart failure.

The references S1 - S22 can be found in the online supplement.

### Traditional approaches

Standard therapy for systolic heart failure is based largely upon the recognition that neurohumoral systems – particularly the renin-angiotensin-aldosterone system and the sympathetic nervous system - are activated in patients with heart failure and contribute to the progression of the disease (s1). The optimal medical regimen targets the peripheral manifestations of these neurohumoral derangements, counteracting vasoconstriction, volume accumulation, and cardiac and vascular remodeling. Thus, conventional therapy consists of angiotensin converting enzyme (ACE) inhibitors, angiotensin type-1 (AT<sub>1</sub>) receptor blockers, and mineralocorticoid receptor (MR) antagonists to reduce the effects of angiotensin II (ANG II) and aldosterone (ALDO) on the heart, blood vessels and kidneys; loop diuretics and ultrafiltration to control the effects of ANG II, ALDO, and sympathetic nerve activity (SNA) on renal handling of sodium and water; and beta-blockers to counter the effects of persistent augmented sympathetic drive on cardiac function. Ancillary therapies not specifically based on neurohumoral dysfunction but likely to ameliorate it include inotropic agents (e.g., digoxin, milrinone) and vasodilators (e.g., hydralazine, isosorbide dinitrate, nitroprusside). We also have device therapy with cardiac resynchronization therapy to improve cardiac output, implantable cardioverter defibrillators to protect against sudden death, and, as a last resort for some patients, cardiac transplantation.

Many of the drugs in common usage – e.g., ACE-inhibitors, MR antagonists, beta-blockers - have proven effective in large clinical trials, but their application in clinical practice is

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frequently limited, especially in the sickest patients who need them most, by serious side effects including hypotension, hyperkalemia, and declining renal function. Some approaches – e.g., aggressive diuresis – may even exacerbate the heart failure syndrome. New ways to intervene in this devastating disease process are clearly needed.

## The central nervous system in heart failure

The peripheral manifestations of neurohumoral excitation in heart failure are paralleled by, and in large part facilitated by, excitatory and inflammatory events in the central nervous system. Recent experimental work has focused on how these neurochemical changes in the central nervous system contribute to the pathophysiology of heart failure.

## Cardiovascular regulatory regions of the brain

Several regions of the brain (Figure 1) have attracted attention because of their relevance to the physiological derangements observed in heart failure: 1) the circumventricular organs of the lamina terminalis – the subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT) - that lack a tight blood-brain barrier and can therefore sense the ambient level of circulating hormones like ANG II; 2) the paraventricular nucleus (PVN) of the hypothalamus, a forebrain nucleus that integrates and responds to a variety of neural and humoral signals regulating sympathetic drive and extracellular fluid volume (s2); and 3) the rostral ventrolateral medulla (RVLM), a point of convergence for signals from forebrain and hindbrain centers that determines the intensity of sympathetic activity (s3).

The SFO and OVLT are concerned primarily with thirst and sodium appetite (s4), behaviors that adversely affect volume regulation in heart failure. The PVN and RVLM contain neurons with long descending axons that innervate the preganglionic sympathetic neurons in the intermediolateral cell column (IML) of the spinal cord (s5), ultimately affecting sympathetic drive to the heart and the vascular tree and, importantly, renal handling of sodium and water and renin release (s6). In addition, the PVN has specialized neurons that regulate the release of adrenocorticotropic hormone (ACTH) and arginine vasopressin (AVP), humoral factors that may contribute to sodium accumulation and vasoconstriction in heart failure. All three regions respond to altered conditions in the periphery in heart failure: the circumventricular organs via humoral cues (e.g., ANG II), the PVN and the RVLM via input from sensory receptors in the heart and vascular tree. In heart failure, the balance of signals from the periphery favors excitation of neurons in all three regions (Figure 2), resulting in volume accumulation and peripheral vasoconstriction. Peripheral consequences of central neural activation in animal models of heart failure include increased sodium consumption and augmented sympathetic drive (1,2) with decreased renal excretion of sodium and water (1,2) and worsening left ventricular dysfunction (3).

## Angiotensin and aldosterone

In heart failure, the neurochemical milieu in the brain mirrors that in the periphery. Here again, the renin-angiotensin system plays a dominant role. Activity of the intrinsic brain renin-angiotensin system (s7) is exaggerated. In the PVN, angiotensin converting enzyme (ACE) activity, which converts angiotensin I to ANG II, is upregulated.(4) ANG II type-1 (AT<sub>1</sub>) receptors that mediate the central nervous system effects of ANG II are increased in the PVN (4,5), the SFO (5) and the RVLM (6). ANG II type-2 (AT<sub>2</sub>) receptors, that appear to modulate the excitatory effects of ANG II on AT<sub>1</sub> receptors (s8), are downregulated in the RVLM in heart failure (7). In acute studies, the abnormalities in central processing of cardiovascular reflexes in animals with heart failure are normalized by blocking brain AT<sub>1</sub> receptors (8-10); unfortunately, an effort to stimulate AT<sub>2</sub> receptors was not effective (7). Chronic intracerebroventricular (ICV) administration of an AT<sub>1</sub> receptor blocker or an ACE inhibitor

reduces sympathetic nerve activity (1,11) and improves volume regulation (1) in animals with heart failure.

ALDO crosses the blood-brain barrier from the circulation, though in restricted quantities, and is also synthesized in brain tissue (12-14). Like ANG II, ALDO acts within the brain to stimulate sodium appetite (s4) and sympathetic drive (s9). Exactly how ALDO effects these central actions remains under investigation. In peripheral tissues, ALDO has genomic effects mediated by activation of cytosolic MR that are protected from binding with corticosterone by activity of the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 2, and non-genomic actions that are partially or completely independent of classical ALDO-sensitive MR (14). ICV administration of an MR antagonist, like ICV administration of an AT<sub>1</sub> receptor blocker or an ACE inhibitor, reduces sympathetic activity and improves volume regulation in animals with heart failure (2). ANG II and ALDO may share a common effector mechanism: both can increase NAD(P)H oxidase activity to produce superoxide (6,15), ALDO likely via a non-genomic mechanism (15). NAD(P)H oxidase-dependent superoxide generation has been implicated as an important factor driving sympathetic activity in animals with heart failure (6,16).

### The pro-inflammatory cytokines

The pro-inflammatory cytokines tumor necrosis factor - alpha (TNF- $\alpha$ ) and interleukin-1 beta (IL-1 $\beta$ ) also activate the central nervous system to increase sympathetic drive in heart failure, but by a different mechanism (s10, 17). TNF- $\alpha$  and IL-1 $\beta$  induce cyclooxygenase-2 (COX-2) activity in perivascular macrophages of the blood-brain barrier (18), generating prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) which enters the brain (19) and stimulates PVN neurons regulating ACTH release (17) and sympathetic drive (20). TNF- $\alpha$  and IL-1 $\beta$  levels increase in the brain as well as in the periphery in heart failure (21,22). The increase in pro-inflammatory cytokines may be linked to changes in the brain renin-angiotensin system - in other tissues, activation of AT<sub>1</sub> receptors induces and activation of AT<sub>2</sub> receptors inhibits the expression of pro-inflammatory cytokines (s11, 23). The presence of pro-inflammatory cytokines in brain tissues is functionally significant, not just a marker of inflammation. Thus, in rats with heart failure, inhibiting brain synthesis of pro-inflammatory cytokines (22), or countering their effects with an anti-inflammatory cytokine (24), reduces COX-2 expression in perivascular macrophages, PGE<sub>2</sub> levels in the cerebrospinal fluid and plasma norepinephrine, an indicator of sympathetic nerve activity. It is particularly interesting that the pro-inflammatory cytokines, like ANG II and ALDO, stimulate NAD(P)H oxidase-dependent superoxide production in the brain (22). Thus, the pro-inflammatory cytokines may contribute to sympathetic drive via both PGE<sub>2</sub> dependent and NAD(P)H oxidase dependent mechanisms.

### Cell signaling

Since NAD(P)H oxidase-dependent superoxide generation is common to several mechanisms leading to sympathetic excitation, it is of interest to consider the downstream molecular events that might ultimately effect an increase in sympathetic drive. Recent data suggest that mitogen-activated protein kinase (MAPK) signaling pathways may play such a role. ANG II, ALDO and the pro-inflammatory cytokines share the ability to stimulate the three major MAPK signaling pathways – p44/42 MAPK, p38 MAPK and JNK – all of which are NAD(P)H oxidase dependent (s12). In heart failure, these three MAPK pathways are activated in the PVN, correlating with superoxide production and neuronal excitation (5). Blocking the p44/42 MAPK pathway substantially reduces sympathetic nerve activity in rats with established HF (Figure 3), but not in sham-operated control rats (25). Notably, MAPK signaling leads to the generation of activator protein-1, which has been implicated as a possible factor in the upregulation of brain AT<sub>1</sub> receptors (26).

## Therapeutic targets in the brain

These experimental studies suggest that interventions at the central nervous system level are beneficial in heart failure. ANG II, AT<sub>1</sub> and AT<sub>2</sub> receptors, ALDO and ALDO-sensitive MR, the pro-inflammatory cytokines, NAD(P)H oxidase, COX-2, and MAPK all appear to be potential targets for central interventions that might substantially reduce the adverse peripheral effects of sympathetic nerve activity in heart failure. In a direct comparison of chronic peripheral versus central administration of an AT<sub>1</sub> receptor blocker in rats with heart failure, the central intervention was actually more effective in reducing left ventricular remodeling following a small myocardial infarction (27). In other studies, chronic central administration of an MR antagonist reduced sodium consumption, normalized renal handling of sodium and water (2), improved baroreceptor regulation of sympathetic nerve activity (2), and reduced circulating levels of pro-inflammatory cytokines (28). Similar effects on sympathetic drive and volume regulation were observed when heart failure rats were treated chronically with an ACE inhibitor (1). Finally, chronic central administration of a cytokine synthesis inhibitor to heart failure rats reduced not only the PVN expression of TNF- $\alpha$  and IL-1 $\beta$ , but also the PVN expression of ACE and AT<sub>1</sub> receptors, the superoxide production in the PVN, COX-2 expression in the microvasculature of the PVN, PGE<sub>2</sub> in CSF, and plasma ACTH and norepinephrine (22).

Brain mechanisms may be attractive targets for therapeutic intervention in heart failure, but they are not so readily accessible in patients. Systemically administered ACE inhibitors in doses that patients can tolerate are unlikely to penetrate the blood-brain barrier in effective concentrations (s13). In theory, ACE inhibitors may even cause harm, since ANG I levels increase (s14) to provide even more substrate for conversion of ANG I to ANG II in the circumventricular organs where ACE concentrations are very high (s15). AT<sub>1</sub> receptor antagonists may cross the blood-brain barrier to varying extents (29), but the doses that can be administered are likely to be limited by effects on blood pressure. Whether the beneficial central effects of MR antagonists observed in animals can be achieved in humans using doses that do not induce hyperkalemia remains to be determined. Though animal studies suggest that inhibiting PGE<sub>2</sub> synthesis in the perivascular cells of the blood-brain barrier would have a desirable effect, systemically administered COX-2 inhibitors have adverse effects in heart failure (s16). Intuitively, antioxidants would seem to be a logical approach, since superoxide production is a key factor driving sympathetic activity. Unfortunately, despite the effectiveness of central antioxidant therapy in animal models, systemic antioxidant therapy in cardiovascular disease has not met with clinical success (s17).

At present, the best hope for minimizing the effects of the brain in heart failure may be to reduce the levels of the key offending hormones. Ongoing investigations with renin inhibitors (30) and aldosterone synthase inhibitors (31) will address that hypothesis. Recent data from our laboratory suggest that blood-borne ANG II contributes to upregulation of AT<sub>1</sub> receptors inside the blood-brain barrier, in the PVN, and thus predicts a beneficial central effect of lowering circulating ANG II (32). Since ANG II is a primary stimulus for adrenal release of ALDO, a secondary benefit of renin inhibition may be a reduction in plasma ALDO. Efforts to reduce circulating pro-inflammatory cytokines with recombinant human soluble tumor necrosis factor- $\alpha$  receptors have been ineffective (s18) and even potentially hazardous (s19). However, systemic treatment with the cytokine synthesis inhibitor pentoxifylline, which is in common use for other indications with minimal side effects, has been very effective in animal studies (21,33,34) and in some (s20, s21) but not all (s22) clinical studies in patients with heart failure. Pentoxifylline readily crosses the blood-brain barrier, so systemically administered drug might reduce both circulating and brain levels of pro-inflammatory cytokines. Finally, in an animal study a systemically administered MR antagonist had the surprising effect of reducing circulating cytokines (33), suggesting a combined approach to mineralocorticoid

receptor blockade and anti-cytokine therapy. The general approach of reducing the levels of humoral factors that activate the central nervous system has the obvious advantage of simultaneously treating their adverse effects on peripheral tissues. Moreover, because of the “crosstalk” that has been observed among central neurochemical systems (22,34), one might anticipate that modifying the activity of one may secondarily mollify another.

In future, the development of drugs that readily cross the blood-brain barrier (35) or preferentially target neural tissues might better address the central nervous system mechanisms contributing to heart failure in humans. Newer technologies - viral vectors (36) or perhaps nanoparticles (37) – hold promise for more specific tissue- or molecule-directed drug therapy. The experimental data presented here suggest that selective treatment of the central nervous system may mimic the improvements now seen with systemically administered drugs, without the associated systemic side effects. However, until new and more selective modes of drug delivery are developed it will not be possible to compare the effects of central versus peripheral interventions, or to evaluate the possible synergistic effects of simultaneous treatment of both facets of the disease.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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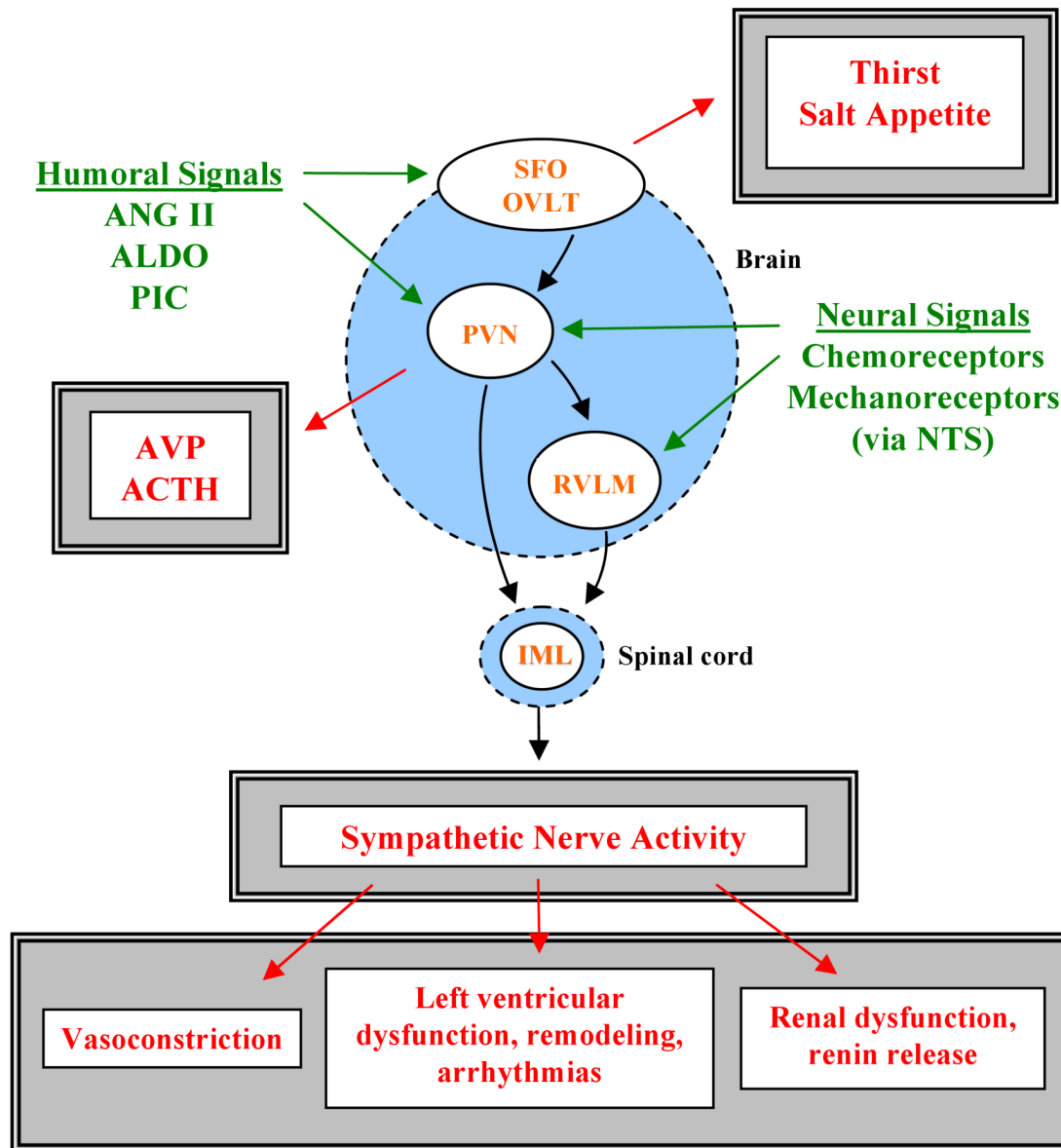
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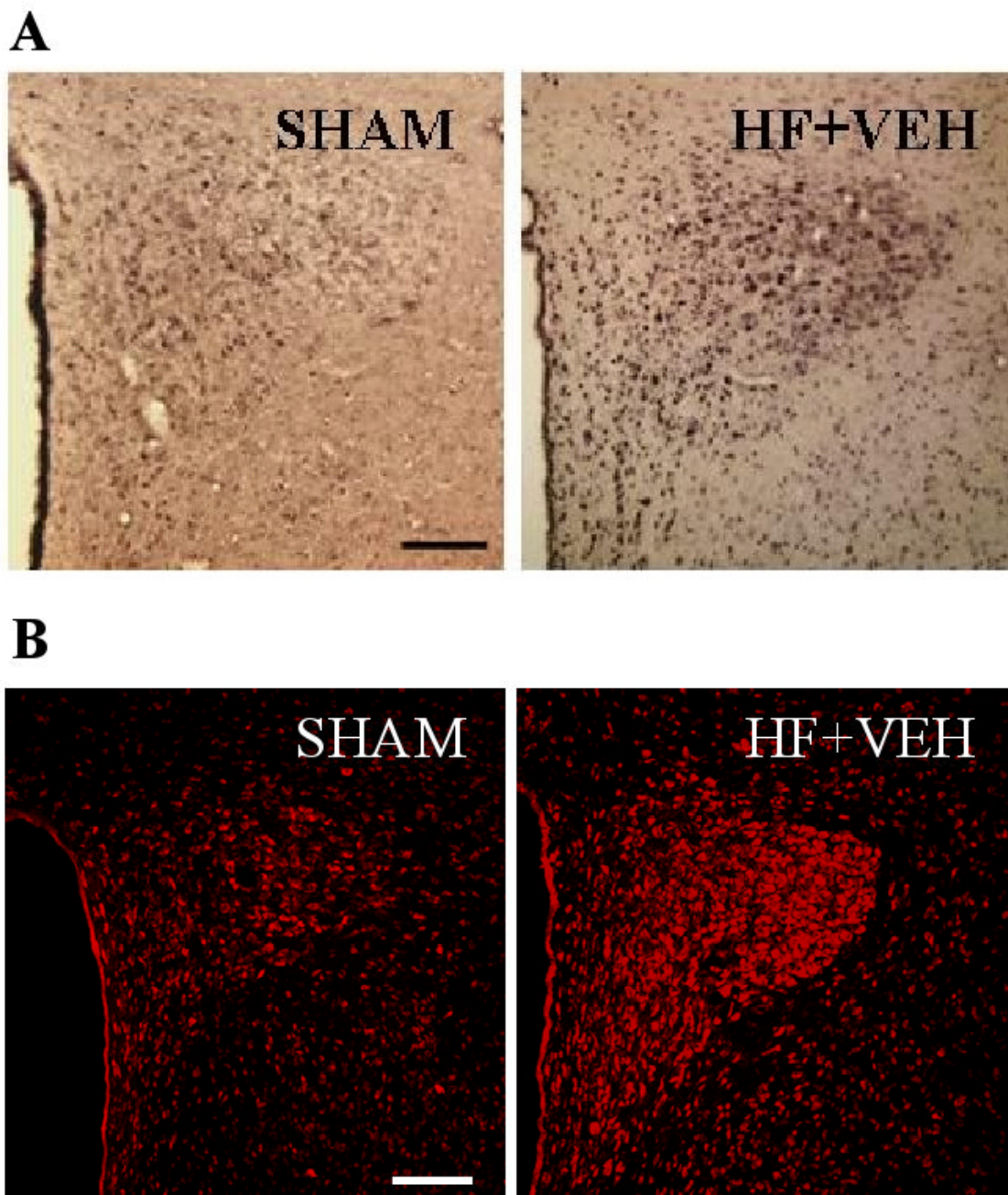
## Central Nervous System Influences in Heart Failure



**Figure 1.**

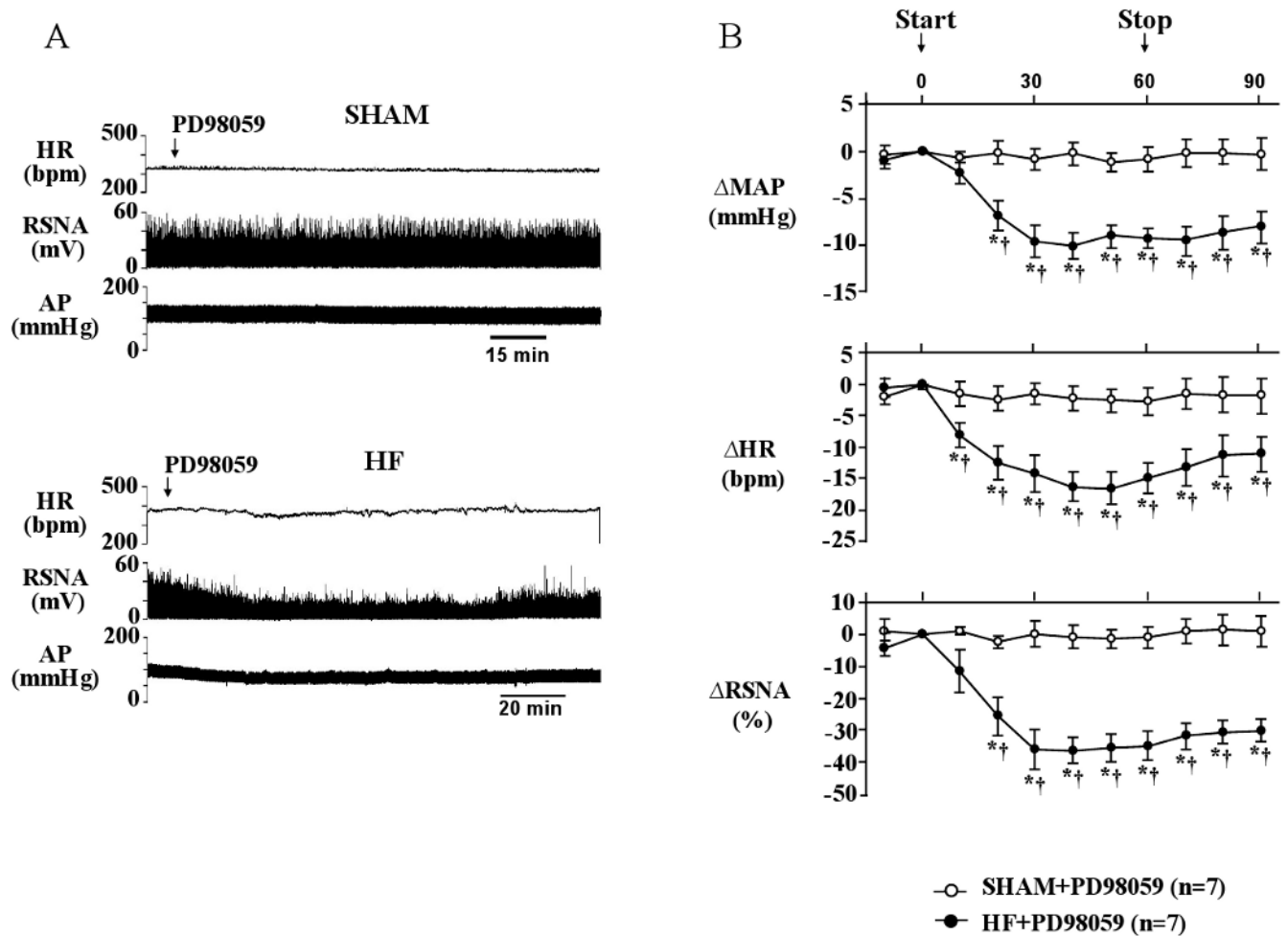
Schematic depicting selected neural and humoral signals impinging upon the central nervous system (green), key effector nuclei (orange), and behavioral and autonomic responses (red). See text for explanation. Detailed pathways are not shown, but are described in references provided in the online supplement. Abbreviations: SFO, subfornical organ; OVLT, organum vasculosum of the lamina terminalis; PVN, paraventricular nucleus; RVLM, rostral ventrolateral medulla; IML, intermediolateral cell column; NTS, nucleus tractus solitarius; AVP, arginine vasopressin; ACTH, adrenocorticotropic hormone; PIC, pro-inflammatory cytokines.





**Figure 2.**

Activation of the central nervous system in heart failure. Coronal (unilateral) sections of the hypothalamic paraventricular nucleus (PVN) from rats with heart failure (HF) of 4 weeks duration and sham-operated controls (SHAM). A) Chronic excitation of PVN neurons is indicated by Fra-Like activity (black dots). B) Superoxide production in PVN neurons is indicated by dihydroethidium fluorescence (red). Superoxide production and neuronal excitation are increased in the PVN and in other cardiovascular regions (not shown) in rats with HF. The HF rats in this study had received chronic intracerebroventricular (ICV) infusions of vehicle (VEH), but no other treatment. In all images, the third ventricle is to the left. Bar=200 microns. Figure adapted from reference (12), and reprinted courtesy of Hypertension.



**Figure 3.**

MAPK signaling and sympathetic excitation in heart failure. A) Representative recordings from a sham-operated (SHAM) rat (top panel) and a rat with heart failure (HF) of 4 weeks duration (bottom panel). An intracerebroventricular infusion of the selective p44/42 MAPK inhibitor PD98059 reduced heart rate (HR, beats/min (bpm)), renal sympathetic nerve activity (RSNA, integrated voltage (mV)) and arterial pressure (AP (mmHg)) in the HF rat, but had no effect on the SHAM rat. B) Grouped data, demonstrating that the p44/42 MAPK inhibitor substantially reduced sympathetic drive in rats with established HF. \* $P < 0.05$  vs baseline; † $P < 0.05$  vs SHAM. The data suggest that p44/42 MAPK is activated in HF and contributes to the sustained increase in sympathetic nerve activity typical of the HF syndrome. p38 MAPK and JNK inhibitors had no effect. Figure adapted from (25), and reprinted courtesy of Hypertension.