Time and Technology Will Tell

The Pathophysiologic Basis of Neurohormonal Modulation in Heart Failure

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KEYWORDS

• Heart failure • Sympathetic nervous system • Renin-angiotensin system • Drug therapy
• Physiology • Neurotransmitter agents • Adrenergic beta-antagonists
• Angiotensin-converting enzyme inhibitors

KEY POINTS

- Neurohormonal abnormalities are central to the pathobiology of heart failure and antagonism of their systemic effects is the basis of contemporary heart failure pharmacotherapy.
- β-Blockers likely confer benefit through induction of reverse remodeling, reduction of sudden cardiac death, and restoration of adaptive adrenergic signaling.
- Antagonists of the renin-angiotensin-aldosterone system have beneficial activities in cells of the heart in addition to their effects in the kidneys and peripheral vasculature.
- All agents that improve survival in heart failure target neurohormones, but not all neurohormonal modulators improve survival.

Healers have been treating heart failure (HF) for millennia, but the central role of neurohormonal abnormalities in its pathogenesis and management was discovered only recently.[1] HF previously was understood almost entirely as the result of structural and functional abnormalities of the heart. In the eighteenth century, anatomists described gross enlargement of failing hearts removed at autopsy, and concluded rightly that hypertrophy was central to the pathobiology of HF. Technological advances in the early twentieth century permitted evaluation of the beating heart, and the field of cardiac physiology evolved. As a result, HF came to be conceived in mechanical terms: the fundamental insult in the failing heart was impaired contractility, and this abnormality was either exacerbated or alleviated by alterations in load. Structure and function reconciled well in animal physiology laboratories, because the hypertrophied and failing heart both resulted from and led to altered loading conditions.

The essential role of neurohormonal disturbances in human HF was recognized first in the 1970s and brought to prominence in the 1980s and 1990s.[2] In this conception of HF, circulating substances synthesized in the heart, kidneys, adrenal glands, and pituitary glands engendered the characteristic anatomic and physiologic abnormalities described by earlier researchers. HF was no longer simply a disease of the heart.

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Increased levels of aldosterone and vasopressin explained the chronically increased preload in the failing heart; norepinephrine and angiotensin (Ang) II induced pathologic hypertrophy and detrimental increases in afterload.

Randomized clinical trials (another important technological advance) reinforced the neurohormonal paradigm. In 1987, the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) showed a 31% reduction in 1-year mortality in patients with end-stage HF treated with the angiotensin-converting enzyme (ACE) inhibitor, enalapril, confirming the importance of Ang II in the progression of HF.[3] The use of beta-adrenergic receptor blockers (β-blockers) in HF was described first in 1981,[4] although the first large mortality trial of β-blockers in HF was the MDC (Metoprolol in Dilated Cardiomyopathy) trial, published in 1993.[5] MDC was followed in the next decade by the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure), the US Carvedilol HF trials, CIBIS (Cardiac Insufficiency Bisoprolol Study) I and II, and COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial, collectively proving that β-blockers improve survival in HF (reviewed in Ref.[6]).

In many respects, clinical trial data have provided the strongest endorsement of the neurohormonal paradigm. Drugs that alter hemodynamic parameters without blocking neurohormonal activation, including digoxin,[7] non–potassium-sparing diuretics,[8] and positive inotropes,[9] have either neutral or negative effects on survival. In this respect, the contemporary use of neurohormonal modulators for HF pharmacotherapy offers an excellent example of reciprocity in translational science: elucidation of basic pathophysiology directs therapeutic targeting, and clinical trial results further inform the understanding of drug mechanism. This article discusses mechanisms of action for neurohormonal antagonists, with attention to both fundamental physiology and clinical trial outcomes.

THE SYMPATHETIC NERVOUS SYSTEM AND CARDIOVASCULAR PHYSIOLOGY

The sympathetic nervous system (SNS) is activated via arterial and venous baroreceptors and arterial chemoreceptors in response to decreases in perfusion pressure or oxygen delivery. In response, efferent fibers increase the release of norepinephrine (NE) (80%) or epinephrine (EPI) (20%) from synaptic varicosities in the myocardium and blood vessels, and stimulate the adrenal medulla to release NE (20%) and EPI (80%) into the blood. These hormones bind at least 9 different subtypes of adrenergic receptors (ARs) (3 beta-ARs [β1, β2, β3], 3 alpha-1 ARs [α1A, α1B, α1D], and 3 alpha-2 ARs [α2A, α2B, α2C]) that are expressed variably by most cell types in the cardiovascular system and function primarily through G protein–coupled signaling cascades (**Fig. 1**).[10]

β1-ARs predominate in the myocardium (70%–80% of total β-ARs), whereas β2-ARs and β3-ARs are less abundant (15%–18% and 2%–3% respectively) (see **Fig. 1**A).[11] The predominant β-AR in vascular tissue is β2-AR, which mediates vasorelaxation (see **Fig. 1**B). Stimulation of β1-ARs on cardiomyocytes activates stimulatory G protein (Gs) and protein kinase A (PKA), leading to increased contractility (via activation of L-type calcium channels and ryanodine receptors); heart rate (via stimulation of L-type calcium channels and hyperpolarization-activated cyclic nucleotide-gated [HCN] channels); and rate of relaxation (via indirect stimulation of sarcoplasmic/endoplasmic reticulum calcium ATPase [SERCA] and Na/K-ATPase). Cardiomyocyte β2-AR activation also increases inotropy, although these receptors are less abundant and have a lower affinity for NE. The β2 is the predominant AR on cardiac fibroblasts, in which it likely plays important roles in HF pathobiology. β3-ARs exert an exclusively negative inotropic effect through activation of nitric oxide.[12]

α1-ARs are best known for their effects in vascular smooth muscle, where they promote vasoconstriction through activation of G_q, although myocardial α1-ARs mediate broadly beneficial effects, including positive inotropy, physiologic cardiomyocyte hypertrophy, and protection from cell death.[13] α2-ARs are predominantly found in presynaptic terminals of adrenergic neurons and adrenal chromaffin cells, where they inhibit NE/EPI release via G_i-related signaling cascades that inhibit PKA activation.[11,14] In this respect, α2-ARs negatively regulate excess NE/EPI release and spillover in both central and peripheral adrenergic synapses.

THE SNS AND HF PATHOPHYSIOLOGY

Chronic catecholamine excess is central to the pathobiology of HF, and the degree of activation is directly proportional to disease severity.[15,16] SNS upregulation also extends to the central nervous system, where NE spillover and turnover is increased.[17,18] In the periphery, SNS upregulation is organ specific: it is preferentially activated in cardiac tissue in mild to moderate HF, and only becomes activated in the kidney and other organ systems in severe HF.[19,20]