The Sympathetic Nervous System and Heart Failure

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KEYWORDS

• Heart failure • Sympathetic nervous system • Neurohormone • Renin-angiotensin-aldosterone

KEY POINTS

- Heart failure is a syndrome characterized by upregulation of the sympathetic nervous system and abnormal responsiveness of the parasympathetic nervous system.
- Hyperactivity of the sympathetic nervous system is triggered by both central and peripheral pathways that are associated with abnormal cardiovascular reflexes observed in a variety of disease states such as cardiac ischemia, ventricular dysfunction, renal failure, and obstructive sleep apnea.
- The renin-angiotensin aldosterone axis is the major regulator of the sympathetic nervous system in the brain.
- Sympathetic hyperactivity in heart failure leads to specific adverse effects which worsen the disease process including adverse remodeling, alteration of the beta adrenergic receptor system, and skeletal muscle abnormalities.
- The parasympathetic nervous system is also altered in heart failure with resulting adverse effects.

INTRODUCTION

Heart failure (HF) is a syndrome characterized by upregulation of the sympathetic nervous system and abnormal responsiveness of the parasympathetic nervous system.[1] Evidence for this dysregulation has included the demonstration of abnormalities in HF patients, including increased urinary catecholamine levels, increased plasma norepinephrine, increased sympathetic tone, and abnormalities in cardiovascular reflexes. Later studies showed that the degree of sympathetic activation as measured by plasma norepinephrine levels correlated with New York Heart Association (NYHA) functional capacity and prognosis, with higher levels portending a worse outcome and NYHA class.[2] The 1980s and 1990s witnessed the development of the neurohormonal hypothesis of HF, and the demonstration that inhibition of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors improved symptoms and mortality in HF resulting from systolic dysfunction. These events shifted the paradigm of treating HF and provided a framework to consider the use of β-blockers for HF therapy, contrary to the prevailing wisdom of the time. Against this backdrop, this article reviews the contemporary understanding of the sympathetic nervous system and the failing heart.

THE AUTONOMIC NERVOUS SYSTEM AND THE HEART

The sympathetic nervous system (SNS) has a wide variety of cardiovascular effects, including heart-rate acceleration, increased cardiac contractility, reduced venous capacitance, and peripheral vasoconstriction.[1,3] Conversely, the parasympathetic nervous system affects the cardiovascular system by slowing the heart rate through vagal innervation.[4]

The authors have nothing to disclose.

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Anatomy

Cardiac sympathetic nerve fibers travel along coronary arteries at the subepicardial level, predominantly in the ventricles.[3] The cardiac parasympathetic nerve fibers run with the vagal nerve subendocardially after crossing the atrioventricular groove, and are abundant mainly in atrial myocardium and less so in the ventricle myocardium.[5]

Physiology

Four categories of the physiologic effects are observed after SNS activation.[6] (1) Norepinephrine (NE) released from neurons via the left stellate ganglions reaches the left ventricles, leading to an increase in contractile strength and blood pressure; NE released from neurons via the right stellate ganglion increases heart rate and shortens atrioventricular conduction via the sinus and atrioventricular nodes. (2) Epinephrine released into circulation by the adrenal cortex exerts effects on both the myocardium and peripheral vessels. (3) Locally released epinephrine and NE have direct effects on peripheral vessels. (4) Circulating norepinephrine acts in multiple locations, such as to increase heart rate during exercise of heart-transplant recipients who lack adrenergic innervation to the cardiac allograft.

Receptors

Norepinephrine and epinephrine released by components of the sympathetic nerve system bind to specific adrenergic receptors (ARs). All ARs are proteins embedded in the cell membrane with 7 transmembrane structures, coupling to heterotrimeric G proteins (Fig. 1). β-Receptor density displays a gradient, greatest at the apex and decreasing toward the base. There are a total of 9 different AR subtypes including 3 α1-receptors, 3 α2-receptors, and 3 β-receptors (β1, β2, and β3).[7] The human heart contains mainly β1, β2, and β3 receptors.[7] Activation of β1- and β2-ARs is the most powerful physiologic mechanism to acutely increase cardiac performance via positive inotropic, dromotropic, and chronotropic effects. β1-ARs activate G_s proteins, whereas β2-ARs couple both G_i and G_s proteins. G_s signaling acts as a "receptor accelerator" and G_i signaling acts as a "receptor brake."[8] The human heart also expresses α1-ARs at low levels (about 20%), but its role in physiologic conditions is unknown.[9]

REFLEX MECHANISM OF SYMPATHETIC HYPERACTIVITY IN HEART FAILURE

Afferent Pathways

Our present understanding of the complex mechanisms engaged by HF arises primarily from the application of NE kinetic methods, which quantify the spillover into plasma from total body, cardiac, renal, brain, or forearm NE production, and from microneurographic recordings obtained from sympathetic fibers innervating muscle or cutaneous vascular beds.[3,10,11] The latter technology refers to muscle sympathetic nerve activity (MSNA), which is a real-time measure of sympathetic nerve activity characterized by inserting a tungsten microelectrode into the muscle fascicle of the innervating peripheral nerve. Based on animal and human studies, the main reflex responses originate from the following afferent pathways (Fig. 2):

- Aortic arch and carotid baroreceptors (SNS inhibition)

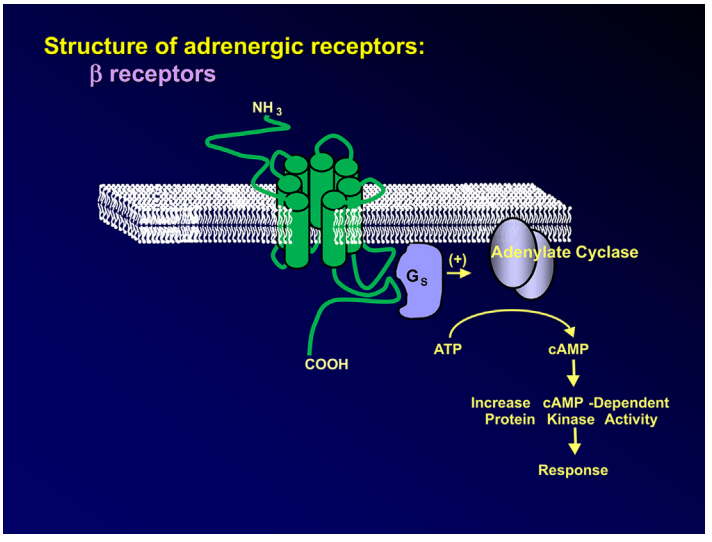

Fig. 1. β-Receptors are G-protein–coupled receptors, and they act by activating a G_s protein. G_s activates adenylyl cyclase, leading to an increase in levels of intracellular cyclic adenosine monophosphate (cAMP). Increased cAMP activates protein kinase A, which phosphorylates cellular proteins. ATP, adenosine triphosphate.