Current Concepts of Neurohormonal Activation in Heart Failure
Mediators and Mechanisms

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ABSTRACT
Neurohormonal activation is a commonly cited array of phenomena in the body's physiologic response to heart failure. Although various neurohormones and pharmacologic agents that moderate their pathophysiologic effects have been reviewed in the nursing literature, both the mechanisms of neurohormonal system activation and cellular and organ system effects have been described only in brief. Accordingly, this article reviews mechanisms of neurohormonal activation and describes cellular and cardiovascular effects of the (1) sympathetic nervous system, (2) renin-angiotensin-aldosterone system, (3) kallikrein-kininogen-kinin system, (4) vasopressinergic system, (5) natriuretic peptide systems, and (6) endothelin in the context of heart failure. This article implicitly details the physiologic basis for numerous current and potential future pharmacologic agents used in the management of heart failure. It is intended that this article be used as a reference for advanced clinical nursing practice, research, and education.

Keywords: cardiac physiology, heart failure, neurohormonal activation

Neurohormonal Activation in Heart Failure: Mechanisms and Cardiovascular Effects
Heart failure (HF) is a complex syndrome that currently affects more than 5 million Americans.¹ The preclinical signs and clinical manifestations of HF are evidence of both ventricular dysfunction and the (initially compensatory) activation of numerous neurohormonal systems. Since original observations of the deleterious effects of neurohormones in the pathophysiology of HF,² the field has grown in knowledge of cellular mechanisms and mediators. A sophisticated understanding of neurohormonal activation in HF is essential to contemporary advanced practice nursing for 5 important reasons. First, basic research increasingly elucidates the mechanisms by which chronic activation of many neurohormonal systems causes further cardiovascular dysfunction in HF. Second, hormone assays are now commonly used in the assessment and diagnosis of persons with HF and in applied clinical research. Third, pharmacologic agents currently used in the management of HF target specific components of neurohormonal systems. Future HF management strategies will likely focus on specific aspects of neurohormonal systems, including targeting intracellular second messenger systems. (See Tables 1–3 for a glossary of key terms and for details about anatomic structures and the major mediators of neurohormonal activation in HF.)

Accordingly, the purpose of this review is to describe the mechanisms of neurohormonal activation and to provide a detailed description of the cellular and cardiovascular effects of the major neurohormonal systems involved in the pathophysiology of HF. The purpose of this review is to describe the mechanisms of neurohormonal activation and to provide a detailed description of the cellular and cardiovascular effects of the major neurohormonal systems involved in the pathophysiology of HF.

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of cellular and cardiovascular effects of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), kallikrein-kininogen-kinin system, vasopressinergic system, natriuretic peptide systems, and endothelin in HF. This review will also serve as a critical reference for advanced practice nurses by providing the physiologic basis for current and future pharmacologic agents used in the management of HF.

**Part I: Sympathetic Nervous System Activation**

The most common characteristics of sympathetic nervous system activation in the cardiovascular system are vasoconstriction, positive chronotropism (increased heart rate), and positive inotropism (increased contractile force of the ventricle). Another important characteristic of sympathetic nervous system activation, particularly in the context of HF, is positive lusitropism (enhanced ventricular relaxation). In response to the ventricular dysfunction of HF, these sympathetically mediated cardiovascular changes initially result in a functional hemodynamic response that helps restore cardiac output. Chronic sympathetic nervous system activation, however, increases myocardial oxygen demand, promotes intracellular calcium toxicity, and gives rise to detrimental proliferative effects such as chamber hypertrophy, expression of noncontractile intracellular proteins, and fibrosis. The sum of sympathetic nervous system effects is a major component of HF pathogenesis.

### Table 1: Glossary of Key Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Autocrine</td>
<td>Modulation of a cell by a hormone produced and secreted by that cell</td>
</tr>
<tr>
<td>Baroreceptors</td>
<td>Sensory neurons with nerve endings within blood vessel walls that detect changes in distension or pressure</td>
</tr>
<tr>
<td>Cardioprotection</td>
<td>Delay of cardiac cell death</td>
</tr>
<tr>
<td>Chronotropism</td>
<td>Refers to rate of depolarization of pacemaker cells. Positive chronotropism results in higher heart rate and negative chronotropism results in lower heart rate</td>
</tr>
<tr>
<td>Chemoreceptors</td>
<td>Sensory neurons that detect small changes in plasma solute concentration, such as acid or carbon dioxide</td>
</tr>
<tr>
<td>Constitutive</td>
<td>Occurs at all times and does not require stimulus to induce</td>
</tr>
<tr>
<td>Diastolic depolarization</td>
<td>Slow and automatic phase of a pacemaker cell's activation</td>
</tr>
<tr>
<td>Downregulation</td>
<td>Internalization and degradation of a number of receptors on the cell membrane</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Secretion of a hormone into the bloodstream to travel to target tissues</td>
</tr>
<tr>
<td>Hydrolysis</td>
<td>Splitting a molecule with the addition of water. Hydrolysis of protein mediators can result in smaller peptides that may or may not have biologic effects</td>
</tr>
<tr>
<td>Hyperpolarization</td>
<td>Decrease in the electronic charge of a cell below its normal resting charge</td>
</tr>
<tr>
<td>Inotropism</td>
<td>Refers to contractile force of cardiac cells—positive inotropism reflects greater force of contraction, and negative inotropism reflects a decrease in force of contraction</td>
</tr>
<tr>
<td>Lusitropism</td>
<td>Refers to rate of ventricular relaxation—positive lusitropism means enhanced relaxation and improved chamber filling and negative lusitropism means slower relaxation and impaired filling</td>
</tr>
<tr>
<td>Natriuresis</td>
<td>Elimination of sodium through excretion in the urine</td>
</tr>
<tr>
<td>Paracrine</td>
<td>Refers to the release of hormones that act locally</td>
</tr>
<tr>
<td>Phosphorylation</td>
<td>Chemical addition of a high-energy phosphate group to a target protein to modulate its activity</td>
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</table>
Signaling coordinating autonomic (sympathetic and parasympathetic) control of the cardiovascular system involves a negative feedback loop (Figure 1) including (1) activation of peripheral or central sensory receptors that respond to changes in physiologic conditions, (2) transmission of impulses via afferent nerve fibers to the nucleus tractus solitarius and then to the vasomotor center of the medulla oblongata, (3) appropriate changes in parasympathetic and sympathetic efferent nerve signals, (4) modulated release of neurotransmitters from postganglionic nerve fibers to target tissues, (5) activation of cell membrane receptors, (6) augmentation or inhibition of intracellular processes, and (7) modulation of local or organ systems.9

Mechanisms of Sympathetic Nervous System Stimulation
Baroreceptor Function
Traditionally, arterial underfilling and the subsequent unloading of arterial, or high-pressure, baroreceptors has been described as the dominant trigger for sympathetic activation in HF.9 Arterial baroreceptors are part of a feedback mechanism that also includes input from cardiac chamber and pulmonary venous baroreceptors (cardiopulmonary baroreceptors)10 and chemoreceptors that exist throughout the body.11 Collectively, these receptors and their associated reflexes regulate hemodynamic and physiologic homeostasis. Arterial baroreceptors are nerve endings within the arterial walls of the carotid sinus, aortic arch, and in renal afferent arterioles12 that rapidly respond to changes in arterial pressure.13 Aortic arch baroreceptor afferent fibers project to the brain via the vagus nerve.14 Carotid sinus baroreceptor afferent fibers project to the brain via Hering's nerve and then the glossopharyngeal nerve.14

When arterial blood pressure increases, the baroreceptor firing rate increases proportionately. The increased baroreceptor firing rate is transmitted through the vagi and glossopharyngeal nerves to the nucleus tractus solitarius.12 Second-order neurons then both inhibit the cardiac accelerator and vasoconstrictor centers and stimulate the vagal parasympathetic center (cardiac deceleration center).13 In combination,
### Table 3: Major Mediators of Neurohormonal Activation in Heart Failure

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Predominant Effect</th>
</tr>
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<tbody>
<tr>
<td>Adenylyl cyclase</td>
<td>Enzyme that converts adenosine triphosphate (ATP) into the active second messenger cyclic adenosine monophosphate (cAMP)</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Steroid hormone that binds with receptors in principal cells of the late distal tubule and promotes sodium retention and potassium excretion</td>
</tr>
<tr>
<td>Angiotensin converting enzyme (kininase II)</td>
<td>Enzyme that cleaves angiotensin I to angiotensin II, and it also cleaves bradykinin into its metabolites</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Mediator that acts on angiotensin II receptors to cause vasoconstriction and sodium and water retention in the kidneys</td>
</tr>
<tr>
<td>Angiotensinogen</td>
<td>Precursor protein that is cleaved by renin to form angiotensin I</td>
</tr>
<tr>
<td>Angiotensin I</td>
<td>Protein cleaved by angiotensin-converting enzyme to form angiotensin II</td>
</tr>
<tr>
<td>Arginine vasopressin</td>
<td>Posterior pituitary hormone that acts on vasopressin receptors to promote vasoconstriction and water conservation</td>
</tr>
<tr>
<td>Atrial natriuretic peptide</td>
<td>Hormone of cardiac origin that acts on natriuretic peptide receptors on vascular smooth muscle cells to promote vasodilatation and on renal cells to eliminate sodium and water</td>
</tr>
<tr>
<td>Big endothelin</td>
<td>Precursor protein that is cleaved by endothelin converting enzymes to form endothelin 1</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Peptide mediator that acts on endothelial cell receptors to promote relaxation of adjacent vascular smooth muscle cells</td>
</tr>
<tr>
<td>B-type natriuretic peptide</td>
<td>Peptide hormone that acts on natriuretic peptide receptors on vascular smooth muscle cells to promote vasodilatation and on renal cells to promote elimination of sodium and water</td>
</tr>
<tr>
<td>Corin</td>
<td>Enzyme that splits atrial natriuretic peptide precursor proteins to the active hormone and amino terminal segment</td>
</tr>
<tr>
<td>C-type natriuretic peptide</td>
<td>Peptide hormone that acts intracellularly or locally on natriuretic receptors on vascular smooth muscle cells to promote vasodilatation</td>
</tr>
<tr>
<td>Cyclic adenosine monophosphate</td>
<td>The active intracellular second messenger that activates protein kinase A</td>
</tr>
<tr>
<td>Cyclic guanosine monophosphate</td>
<td>The intracellular second messenger that activates protein kinase G</td>
</tr>
<tr>
<td>Diacylglycerol</td>
<td>The intracellular second messenger that activates protein kinase C</td>
</tr>
<tr>
<td>Endothelin 1</td>
<td>Endothelium-derived peptide that acts on endothelin receptors to cause potent vasoconstriction</td>
</tr>
<tr>
<td>Furin</td>
<td>Enzyme that splits B-type natriuretic peptide precursor proteins to the active hormone and amino terminal segment</td>
</tr>
<tr>
<td>Inositol triphosphate</td>
<td>Intracellular second messenger that activates inositol triphosphate-gated ion channels causing vasoconstriction</td>
</tr>
<tr>
<td>Kallidin</td>
<td>A peptide member of the kinin family, acts on receptors on endothelial cells to promote relaxation of adjacent vascular smooth muscle cells</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>A gas produced by endothelial cells under certain conditions, diffuses to adjacent vascular smooth muscle cells and promotes vasodilatation</td>
</tr>
</tbody>
</table>

(continues)
inhibition of the cardiac accelerator and vasoconstrictor centers and stimulation of the vagal parasympathetic center cause negative chronotropism and inotropism and decrease arterial pressure. Conversely, when arterial blood pressure decreases, the baroreceptor firing rate also decreases. The decreased firing rate is transmitted to the nucleus tractus solitarius. Subsequent signals then stimulate the vasoconstrictor and cardiac accelerator regions of the brain and simultaneously inhibit the vagal parasympathetic center. The net results are vasoconstriction and positive chronotropism, inotropism, and lusitropism, all of which acutely restore arterial blood pressure.

Cardiopulmonary baroreceptors, or low-pressure baroreceptors, exist within the walls of the atria, ventricles, and pulmonary veins. Like other baroreceptors, low-pressure baroreceptors are nerve endings that are sensitive to pressure. Cardiopulmonary baroreceptors also transmit signals to the nucleus tractus solitarius via the vagus nerve. The key difference in low-pressure baroreceptors is that they are sensitive to filling (or venous) pressures instead of arterial pressure. Thus, activation of low-pressure baroreceptors is anticipated in response to a change of blood volume or blood return to the heart as opposed to a change in mean arterial pressure.
In combination, cardiopulmonary and high-pressure baroreceptors control minute-to-minute changes in cardiovascular homeostasis by responding to changes in intravascular fluid volume and pressure.

**Chemoreceptor Function**

Several chemoreceptors and associated chemoreflexes exist in the human body. Chemoreceptors are nerve endings that terminate in highly vascularized areas and are sensitive to changes in plasma chemical concentration. Not surprisingly, the predominant effects of chemoreceptors that respond to changes in plasma oxygen or carbon dioxide levels are mediated through changes in respiratory rate. However, in conditions of low oxygen delivery to tissue, such as in HF, chemoreceptor activation may play a role in modulation of the cardiovascular system.

Central chemoreceptors, located in the brainstem, primarily respond to hypercapnia. Activation of these chemoreceptors is part of the central nervous system ischemic response that gives rise to increased sympathetic activity, including increased respiratory rate, heart rate, and blood pressure. Peripheral chemoreceptors, located in the carotid bodies of the internal carotid arteries and the aortic arch, primarily respond to hypoxia. Similar to baroreceptors, carotid sinus chemoreceptors transmit signals to the medulla by way of Hering’s nerve and the glossopharyngeal nerve, and aortic arch chemoreceptors transmit impulses via the vagi. Peripheral chemoreceptors are highly vascularized and thus are able to detect minute changes in plasma solutes such as oxygen, carbon dioxide, lactic acid, and sodium. The predominant effect of chemoreceptor response to low plasma oxygen or high plasma carbon dioxide is to stimulate an increase in respiratory rate. Acting via the nucleus tractus solitarius and medullary autonomic regions, chemoreceptor stimulation by hypoxia or hypercapnia increases sympathetic outflow to heart and vasculature, resulting in both tachycardia and vasoconstriction.

**Norepinephrine**

Norepinephrine (NE) is a catecholamine that is synthesized and stored in vesicles within sympathetic nervous system fiber terminals. Norepinephrine, among other catecholamines, is also synthesized and released from the adrenal medulla. In neurons, NE synthesis occurs within the axoplasm of terminal nerve endings. The amino acid tyrosine is hydroxylated (addition of a hydroxyl group) to form dihydroxyphenylalanine, which is decarboxylated (removal of a carboxyl group) to form dopamine. Once transported to presynaptic vesicles, further hydroxylation results in NE release. Norepinephrine is hydrophilic; thus, it works by binding to plasma membrane receptors and activating intracellular second messengers. When NE is released from the nerve endings, it binds with one of several adrenergic receptors on the postsynaptic membrane and stimulates a sequence of chemical events. Much of the NE is taken up into the nerve terminal by a reuptake system, but some may spill into the circulation. High levels of plasma NE have been detected in patients with HF and are an independent predictor of mortality in this population.

**Cardiovascular Adrenergic Receptors and Physiologic Consequences of Activation**

**β-Adrenergic Receptors**

In the heart, β-adrenergic receptors predominate and are coupled with a stimulatory G protein. When NE binds with a β-adrenergic receptor (Figure 2), the α subunit of the stimulatory G protein dissociates and increases the activity of the enzyme adenylyl cyclase. Adenylyl cyclase generates cyclic adenosine monophosphate from adenosine triphosphate (ATP). Cyclic adenosine monophosphate acts within cells as the second messenger of NE. In sinoatrial node cells, cyclic adenosine monophosphate interacts directly with sodium ion channels known as funny sodium channels (Na_, or i, channels). Modulation of funny sodium channels by cyclic adenosine monophosphate increases sodium influx during diastolic depolarization, thus increasing heart rate (positive chronotropic mechanism). Cyclic adenosine monophosphate also activates cyclic adenosine monophosphate-dependent protein kinase A (PKA). Protein kinase A acts on intracellular protein targets by adding a high-energy phosphate, a process called phosphorylation. Phosphorylation of target proteins modulates their activity. In pacemaker cells, PKA phosphorylates T-type calcium ion channels, increasing calcium influx during diastolic depolarization (positive chronotropic mechanism). In contractile cells, PKA phosphorylates L-type calcium ion channels, increasing the
amount of intracellular calcium available for cross-bridge formation during systole, leading to a greater force of contraction (positive inotropic mechanism).9

When activated, PKA also phosphorylates a protein called phospholamban on the membrane of the sarcoplasmic reticulum.7 Under normal conditions, phospholamban partially inhibits the actions of an enzyme called sarcoplasmic reticum calcium adenosine triphosphatase (ATPase) (also known as SERCA). Sarcoplasmic reticum calcium ATPase facilitates the reuptake of calcium into the sarcoplasmic reticulum for storage during diastole. Phosphorylation of phospholamban gives rise to enhanced SERCA activity, increasing the rate of calcium removal from the intracellular space.7 This results in an enhanced rate of contractile protein and chamber relaxation, enhancing ventricular filling (lusitropic mechanism).24 β₂-Adrenergic receptors are also located in the juxtaglomerular cells of the kidneys and increase renin release when stimulated.23 The consequences of increased renin release are described in detail in the RAAS section.

Cardiovascular β₂-adrenergic receptors are normally coupled with a stimulatory G protein but may also be coupled with an inhibitory G protein22 (Figure 3). If the α subunit of stimulatory G protein dissociates, the result is positive chronotropism, inotropism, and lusitropism. If the α subunit of the inhibitory G protein dissociates, adenylyl cyclase is inhibited and intracellular pathways that lead to chamber remodeling are activated.22 Stimulation of β₂-adrenergic receptor may either promote positive inotropism, chronotropism, lusitropism, and proliferative effects or exert mixed proliferative and cardioprotective effects.21 That is, stimulatory G protein activity also causes cardiomyocyte apoptosis.21,22 In contrast, inhibitory G protein activity initiates cell survival signaling and inhibits apoptosis.21,22

β₁-Adrenergic receptors are less well described but have been found in the heart.27,24 It is generally accepted that activation of
β-adrenergic receptors results in negative inotropism. When stimulated, β-adrenergic receptors inhibit the actions of adenylyl cyclase by coupling with an inhibitory G protein and activate nitric oxide synthase. Inducible nitric oxide synthase and subsequent nitric oxide production within cardiac cells modulate inotropism by influencing calcium influx via L-type calcium channels. Nitric oxide also alters ryanodine receptor activity. Ryanodine receptors exist within the cytoplasm of cardiac cells and modulate the release of calcium that is stored in the sarcoplasmic reticulum. Ryanodine is one of the cellular proteins that is phosphorylated by PKA in response to –adrenergic stimulation. In response to sympathetic nervous system stimulation, ryanodine phosphorylation contributes to positive inotropism. By blunting the effect of sympathetic nervous system stimulation, nitric oxide produced within the cardiac cell limits both the positive inotropic effects of ryanodine phosphorylation and the positive lusitropic effects of phospholamban phosphorylation.

In summary, NE can exert different effects on cardiac cells depending on the type of β-adrenergic receptor with which it binds and the type of G protein with which the receptor is coupled. Alterations in β receptors and G proteins in the context of HF and chronic management with β-blocking drugs both make the short- and long-term effects of sympathetic stimulation in the failing heart difficult to predict. Sympathetic stimulation acting on β-adrenergic receptors may serve either a cardioprotective or a deleterious function in the failing heart.

α-Adrenergic Receptors
α-adrenergic receptors have widespread distribution on vascular smooth muscle cells and in other tissues, including the heart. When stimulated with NE, α-adrenergic receptors promote contraction of these tissues by increasing intracellular calcium. These receptors are coupled with a third subtype of G protein: Gq. In response to chronic activation, α-adrenergic receptors uncouple from stimulatory

**Figure 3:** B2AR stimulation—B2ARs’ couple with either stimulatory or inhibitory G proteins and can catalyze either stimulation or inhibition of adenylyl cyclase. In the event of Gs coupling, adenylyl cyclase is inhibited and intracellular pathways that cause cell proliferation are activated leading to remodeling and cell survival signals. In the event of Gi coupling, adenylyl cyclase is stimulated to generate cAMP from ATP.

Abbreviations: NE, norepinephrine; B2AR, β2-adrenergic receptor; Gi, inhibitory G protein; Gs, stimulatory G protein; AC, adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate.
G proteins, a process brought about by phosphorylation of receptor subunits by β-adrenergic receptor kinase.28 β-adrenergic receptor kinase only phosphorylates β₁-adrenergic receptors that are occupied by receptor agonists (like NE), preventing the receptor from activating G proteins and facilitating the binding of β-arrestins.26 β-Arrestins are proteins that uncouple receptors from G proteins and, in this context, completely inactivate β₁-adrenergic receptors.26,29 In HF, β₁-adrenergic receptors are thought to couple more with inhibitory G proteins than stimulatory G proteins; thus, adenyl cyclase is frequently inhibited.23 β₁-adrenergic receptor-mediated nitric oxide production may also attenuate the positive inotropic effects of the sympathetic nervous system.20,23

There are detrimental effects of chronic sympathetic nervous system stimulation in HF, including altered adrenergic receptor function. The detrimental effects of chronic sympathetic nervous system activation must also be considered in the context of activation of multiple neurohormonal systems, predominantly RAAS.

**Part II: The RAAS**

The RAAS is essential to the maintenance of fluid and sodium balance and hemodynamic stability.33,34 Moreover, RAAS activation plays an important role in both adaptive and maladaptive mechanisms in response to HF.19 Both the classic model of RAAS and newly identified components of this complex system are presented herein. Elements of the RAAS also exist in several tissue types. Several tissues, including heart, brain, vasculature, adipose tissue, and adrenal glands have all been shown capable of endogenous expression of RAAS mediators.25,34 Juxtaglomerular cells of the renal afferent arterioles are the main source of circulating renin, and hepatocytes are the main source of circulating angiotensinogen, but various tissue RAASs may contribute to the local production of RAAS mediators.

**Renin**

Renin is an enzyme produced and secreted from the juxtaglomerular cells of the renal afferent arterioles.23,34 Within the endoplasmic reticulum of the juxtaglomerular cells, a 401-amino acid precursor protein (preprorenin) is cleaved to

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**Figure 4:** α₁AR activation in vascular smooth muscle. On occupation of the α₁AR with NE, Gq dissociates from the G-protein complex and activates PLC. PLC hydrolyzes PIP₂ into IP₃ and DAG. IP₃ activates IP₃-gated calcium channels on the sarcoplasmic reticulum membrane, triggering calcium release into the cytoplasm. DAG stimulates PKC, which phosphorylates cation (most likely calcium) channels contributing to increased intracellular calcium. DAG also causes proliferative effects.

Abbreviations: NE, norepinephrine; α₁AR, α₁-adrenergic receptor; Gq, type q G protein; PLC, phospholipase C; PIP₂, phosphatidylinositol biphosphate; IP₃, inositol triphosphate; DAG, diacylglycerol; Ca²⁺, calcium; PKC, protein kinase C.
Prorenin is then cleaved by a trypsin-like activating enzyme to form renin. Prorenin is most identifiable as the enzyme that cleaves angiotensinogen. Angiotensinogen is a protein synthesized and secreted by the liver into the circulation where it is cleaved to form angiotensin I (Figure 5). Angiotensin I is then hydrolyzed by angiotensin-converting enzyme (found predominantly in pulmonary capillaries) to form biologically active angiotensin II (ANG II). Active angiotensin II has several known biologic effects, including vasoconstriction and sodium and water retention. Active angiotensin II also has profibrotic and proinflammatory effects that contribute to untoward cardiac chamber remodeling.

**Mechanisms of RAAS Activation**

Renin secretion is controlled by several intrinsic intrarenal mechanisms, in addition to control by the sympathetic nervous system. In the distal thick ascending limb of the loop of Henle, macula densa cells are both electrically and chemically coupled with juxtaglomerular cells of the afferent arterioles by mesangial cells. This coupling promotes an inverse relationship between renal tubular sodium chloride concentration and plasma renin concentration. Decreased tubular lumen sodium chloride concentration facilitates 2 events leading to renin secretion from juxtaglomerular cells. First, decreased sodium chloride uptake from the lumen into the macula densa cells via the sodium-potassium-2 chloride cotransporter increases calcium within macula densa cells. Second, decreased tubular fluid sodium chloride concentration results in decreased ion pumping and ATP consumption, thus reducing the breakdown of ATP to adenosine in macula densa cells.

**Figure 5:** Renin-angiotensin-aldosterone system. Abbreviations: ACE, angiotensin-converting enzyme; AVP, arginine vasopressin; MAP, mean arterial pressure; NE, norepinephrine; Na, sodium.
Adenosine is a known inhibitor of renin release from the juxtaglomerular cells. Thus, renin release from juxtaglomerular cells is favored by either increased prostaglandin E2 or decreased adenosine production by macula densa cells.

A pressure-sensitive mechanism of renin release also exists. In fact, the pressure-sensitive and sodium chloride load mechanisms combined make up what is called tubuloglomerular feedback, which plays an important physiologic and pathophysiologic role in regulating renal hemodynamics. Stretch of the juxtaglomerular cells inhibits renin release and may also interfere with prorenin transcription. Using data from an animal model, researchers found that stretching macula densa cells led to increased adenosine production. Adenosine can diffuse from macula densa cells to vascular smooth muscle cells in the afferent arteriole wall and cause vasoconstriction, inhibiting renin secretion from juxtaglomerular cells.

Sympathetic nervous system activation also stimulates renin release. This response is mediated by activation of β1-adrenergic receptors on the cell surface of juxtaglomerular cells by NE. Cyclic adenosine monophosphate acts as the intracellular second messenger, directly stimulating renin release from secretory granules. In HF, decreased filtered sodium chloride load, decreased renal arterial pressure, and elevated levels of circulating neurohormones (eg, NE), all contribute to increased renin release. As renin is secreted into the circulation (and possibly in selected tissues), it promotes increased levels of angiotensin I, ultimately increasing circulating ANG II.

**Angiotensin II Receptors and the Effects of Activation**

Two ANG II receptor subtypes have been identified: AT1 and AT2. The majority of biologic effects of ANG II expression are mediated via AT1 receptors. AT1 receptors are found on vascular smooth muscle cells and in the heart. AT1 receptors are predominantly Gq-coupled and when occupied activate phospholipase C. Phospholipase C activation leads to the hydrolysis of phosphatidylinositol bisphosphate, stimulation of inositol triphosphate-mediated calcium release from the endoplasmic reticulum, and activation of protein kinase C by diacylglycerol. The result is increased intracellular calcium, increased contractile force, and subsequent vasoconstriction of vascular smooth muscle. In response to chronic activation, AT1 receptors activate intracellular pathways that lead to proliferative cellular remodeling. In HF, not only does ANG II stimulate undesired vasoconstriction but also cellular structural changes that further impair contractile function, including hypertrophy and fibrosis.

Vascular and tubular AT1-receptor activation increases renal sodium and water retention and thereby increases blood volume. First, AT1-receptor activation leads to calcium-mediated vasoconstriction of both afferent and efferent renal arterioles, which decreases renal blood flow and thereby sodium and volume delivery to the glomerulus. Second, vasoconstriction also limits medullary blood flow, favoring passive sodium and water reabsorption in the loop of Henle. In the proximal tubule, AT1-receptor activation enhances luminal sodium-hydrogen exchange and sodium-bicarbonate cotransport and activates sodium-potassium ATPase on the basolateral membrane. In the distal tubule, AT1-receptor activation enhances sodium-hydrogen exchange and epithelial sodium channel activity. All renal actions of AT1-receptor activation thus promote sodium reabsorption and limit sodium elimination, favoring an increase in blood volume.

AT1 receptors are found in several brain regions critical for fluid, electrolyte, and volume homeostasis. Neurons projecting to the supraoptic and paraventricular nuclei and anterior pituitary can stimulate arginine vasopressin secretion from the posterior pituitary. Neurons projecting to the median optic nucleus and subfornical organ can also stimulate thirst. Increased calcium currents due to AT1-receptor activation mediate the neuronal effects of ANG II.

In the cortex of the adrenal gland, zona glomerulosa cells respond to AT1-receptor activation with aldosterone secretion. In fact, in persons with chronically activated RAAS, zona glomerulosa cell hypertrophy is often caused by chronic ANG II stimulation. By activating Gq proteins, AT1-receptor activation leads to increased intracellular calcium. Increased intracellular calcium stimulates aldosterone secretion. Aldosterone binds with renal mineralocorticoid receptors in principal cells of late distal tubule and promotes sodium (and secondarily water) retention.

AT2 receptors are different from AT1 receptors in several ways. First, AT2 receptors are
ubiquitous only at birth, but they are also found in the heart of older humans in disease states like HF. Second, activation of AT2 receptors is thought to be initially cardioprotective. Although the subject of ongoing investigation, AT2-receptor activation is hypothesized to involve activation of a membrane potassium channel (delayed K rectifier), and inactivation of T-type calcium channels. Together, these cause relaxation of vascular smooth muscle and decreased responsiveness to vasoconstrictive substances such as NE. In the heart, AT2-receptor activation may counteract certain AT1-receptor-mediated effects, but it has also been linked with cardiac chamber hypertrophy, fibrosis, and apoptosis.

In summary, although ANG II-receptor activation helps restore arterial pressure by vasoconstriction and water and sodium retention in the acute phase of HF, chronic stimulation of RAAS further perpetuates HF by causing increased blood volume and peripheral vascular resistance and directly triggering cardiac chamber remodeling.

**Modern Model of RAAS**

Decades of research have led to the discovery of several new aspects of RAAS, which is often simplified for clarity (Figure 6). First, the peptide kallikrein can cleave prorenin to renin and cleave angiotensinogen directly to ANG II. Second, other substances, including heart or other tissue chymase enzymes, can cleave angiotensin I to form ANG II. Third, angiotensin-converting enzyme II converts angiotensin I to a metabolite, AT(1–7), with vasoactive properties and a unique receptor. Activation of the AT(1–7) receptor by this metabolite leads to vasodilatation, counteracting the effects of ANG II. Fourth, aldosterone is hypothesized to augment conversion of angiotensin I to ANG II in a positive feedback mechanism. Finally, angiotensin-converting
enzyme also serves to cleave another active peptide bradykinin to its metabolites. Bradykinin, as described in detail in the subsequent text, also has vasodilatory and cardioprotective properties.

**Part III: The Kallikrein-Kininogen-Kinin System**

The kallikrein-kininogen-kinin system is important in the study of HF because of the crossover between the kallikrein-kininogen-kinin system and RAAS and the cardioprotective effects of the biologically active kinins.\(^{52-54}\) Bradykinin and kallidin are formed by an interaction between precursor molecules.\(^{55}\)

**Mechanisms of Kallikrein-Kininogen-Kinin System Activation**

The *kinin system* involves several precursor proteins that are cleaved by proteases to form active mediators, similar to the clotting and angiotensin cascades. Two pathways are included in this system (Figure 7). First, tissue prekallikrein is activated by plasmin or plasma kallikrein to form active tissue kallikrein.\(^{54}\) Active tissue kallikrein releases the vasoactive peptide kallidin from low-molecular-weight kininogen.\(^{52}\) As with angiotensinogen, low-molecular-weight kininogen is synthesized by hepatocytes and secreted into the circulation.\(^{36,54}\) Kallidin is further broken down by an aminopeptidase to form bradykinin.\(^{52}\) Second, hepatocytes also produce plasma prekallikrein, which is converted to active plasma kallikrein by activated Hageman factor (coagulation factor XIIa).\(^{52}\) Active plasma kallikrein then acts to release bradykinin from high-molecular-weight kininogen, a substance also produced primarily in the liver.\(^{52,54}\) Bradykinin is degraded into inactive metabolites by enzymes known as kininases or a neutral endopeptidases.\(^{36,53}\) Most notably, kininase II is the same enzyme as angiotensin-converting enzyme, which is responsible for the conversion of angiotensin I to ANG II. That is, the same enzyme breaks down bradykinin to active and inactive metabolites and converts angiotensin I to ANG II.\(^{52-54}\)

**Kallikrein-Kininogen-Kinin System Receptors and Effects of Activation**

Two kinin receptors have been identified in humans: kinin receptor type 1 (B\(_1\)) and kinin receptor type 2 (B\(_2\)).\(^{52-55}\) The B\(_1\)-kinin receptor is normally not expressed in healthy human tissue but is thought to become significantly active in inflammatory or injury-response conditions.\(^{54}\) In particular, expression of B\(_1\)-kinin receptors in coronary vascular endothelial cells is increased in patients with HF.\(^{56}\) B\(_1\)-kinin receptors have a high affinity for bradykinin metabolites but not bradykinin itself.\(^{52}\) When occupied, B\(_1\)-kinin receptors stimulate G\(_\alpha\)-mediated activation of phospholipase C.\(^{32,54}\) Phospholipase C hydrolyzes phosphatidylinositol biphosphate, which is broken down into inositol triphosphate and diacylglycerol (Figure 8). Inositol triphosphate increases intracellular calcium by activating inositol
triphosphate-gated calcium ion channels on the endoplasmic reticulum.\(^{57}\)

Diaclylglycerol activates protein kinase C\(^{32}\), resulting in the phosphorylation of many intracellular targets that also increase intracellular calcium concentrations. Increased intracellular calcium in endothelial cells promotes the production of nitric oxide and subsequently increases cyclic guanosine monophosphate production in adjacent vascular smooth muscle cells.\(^{53,54,58}\) Elevated levels of cyclic guanosine monophosphate in vascular smooth muscle cells promote vasodilation.\(^{54,57}\) B\(_1\)-kinin receptor stimulation also activates phospholipase A\(_2\), liberating arachidonic acid and its metabolites from the cell membrane.\(^{54,57}\) Important by-products of arachidonic acid are prostaglandins, specifically prostaglandin \(E_2\) and \(I_2\), which may also play a role in adjacent vascular smooth muscle cell relaxation.\(^{54,57}\) Furthermore, the B\(_1\)-kinin receptors are also coupled with inhibitory G proteins\(^{5}\) and can inhibit the actions of adenylyl cyclase.

Although the intracellular signaling of B\(_1\)-kinin receptors and B\(_2\)-kinin receptors is similar, a few key differences are important to note. First, unlike B\(_1\)-kinin receptors, B\(_2\)-kinin receptors are constitutively expressed in healthy individuals and are downregulated in patients with HF.\(^{59}\) Second, the B\(_2\)-kinin receptors have a higher affinity for bradykinin and kallidin,\(^{57,58}\) not bradykinin metabolites. Third, activation of B\(_1\)-kinin receptors results in a sustained increase in intracellular calcium, whereas activation of B\(_2\)-kinin receptors results in a transient increase in intracellular calcium.\(^{54,57}\) Fourth, B\(_2\)-kinin receptors suffer significant desensitization, whereas B\(_1\)-kinin receptors do not.\(^{54,59}\) Finally, B\(_2\)-kinin receptors may directly activate membrane calcium channels and thereby increase intracellular calcium in endothelial cells.\(^{54}\)

Because the kinins and their metabolites are largely viewed as endogenous vasodilators, their role in HF pathogenesis is gaining interest. Under conditions of angiotensin-converting enzyme inhibition and partial blockade of AT\(_1\) receptors, the potential cardioprotective role of bradykinin in HF may be manifested.
Part IV: Natriuretic Peptide System

In 1964, first evidence emerged that the heart is an endocrine organ, producing and expressing endogenous hormones. Since that time, 2 natriuretic hormones have been identified as having a role in HF: atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). These natriuretic peptides play an important regulatory role in volume homeostasis, having several beneficial and cardioprotective effects including natriuresis, vasodilatation, and modulation of both the sympathetic nervous system and RAAS. C-type natriuretic peptide (CNP), a peptide produced by endothelial cells, has also been identified in humans. All natriuretic peptides are continuously secreted but are found in elevated levels in HF cases.

Atrial Natriuretic Peptide

Atrial natriuretic peptide is a biologically active, 28-amino acid hormone that is primarily synthesized by atrial myocytes. Atrial natriuretic peptide is synthesized, stored, and secreted to a lesser extent in healthy ventricular myocytes, although ventricular ANP synthesis increases in HF. It is stored as part of the 126-amino acid precursor protein proANP. When secreted from granules of atrial cells, proANP is split by the enzyme corin into the amino terminal portion, Nt-proANP1–98, and the active hormone ANP99–126. Corin is an enzyme that is produced in both the atrial and ventricular myocytes; however, levels are much greater in the atria. Although they are secreted in equal amounts, the active hormone ANP99–126 has a much shorter half-life than Nt-proANP1–98: 1 to 5 minutes and 40 to 50 minutes, respectively. This is due to a binding of the active hormone to natriuretic peptide receptors and rapid enzymatic degradation by a neutral endopeptidase.

B-Type Natriuretic Peptide

B-type natriuretic peptide is a biologically active, 32-amino acid hormone that is synthesized in both atrial and ventricular myocytes. In fact, in nonfailing hearts more BNP is secreted from the atria than from the ventricles and more ANP is secreted than BNP. Corin is an enzyme that is produced in both the atrial and ventricular myocytes; however, levels are much greater in the atria. Although they are secreted in equal amounts, the active hormone ANP99–126 has a much shorter half-life than Nt-proANP1–98: 1 to 5 minutes and 40 to 50 minutes, respectively. This is due to a binding of the active hormone to natriuretic peptide receptors and rapid enzymatic degradation by a neutral endopeptidase.

C-Type Natriuretic Peptide

C-type natriuretic peptide is synthesized as a 103-amino acid precursor protein: proCNP. ProCNP is cleaved to form an amino terminal fragment and 1 of 2 biologically active peptides: CNP1–51 or CNP1–103. The amino terminal fragments of proCNP (Nt-proCNP1–51 or Nt-proCNP1–76) have longer half-lives, just like the other natriuretic peptides. C-type natriuretic peptide is predominantly an endothelial product and is thought to have more local (paracrine) or intracellular (autocrine) effects than endocrine function. C-type natriuretic peptide is also produced in failing human hearts.

Mechanisms of Natriuretic Peptide Expression

Both ANP and BNP are continuously secreted from the heart, but expression and secretion are increased in response to various stimuli. Constitutive secretion is most likely caused by passive diffusion of the natriuretic peptides from the specific atrial granules that store them. Regulated secretion involves release of the natriuretic peptides from storage granules in response to an agonist, several of which have been identified. Agonists include epinephrine, NE, acetylcholine, arginine vasopressin, endothelin 1, ANG II, and numerous inflammatory cytokines. Natriuretic agonists not only modulate the hemodynamic stimuli for peptide expression but also directly stimulate their release.

The predominant mechanism for ANP and BNP secretion is wall stretch, activating what is known as stretch-secretion coupling. In response to stretch, natriuretic peptides are immediately secreted into the circulation. Storage granules contain more ANP than BNP, so ANP levels show a greater initial increase than BNP in response to acute stretch. Wall stretch also leads to depletion of
stored natriuretic peptides. In chronic wall stretching due to intravascular fluid volume overload, synthesis of natriuretic peptides is enhanced to replace that which was secreted. Induction of natriuretic peptide synthesis and storage gives rise to elevated levels that are seen in patients with HF. Because circulating levels of ANP and BNP reflect the severity of HF, serum levels of BNP and Nt-proBNP are used as diagnostic and prognostic indicators for patients with HF. Elevated levels of active BNP and amino-terminal portions in HF reflect greater synthesis and secretion, less clearance by enzymatic degradation, and less affinity for the natriuretic peptide clearance receptor.

**Natriuretic Peptide Receptors and the Effects of Activation**

Three natriuretic peptide receptors have been identified: type A, type B, and type C. Both type A and B receptors are responsible for the known physiologic and pathophysiologic effects of this system of protein hormones. Atrial natriuretic peptide and BNP preferentially bind to type A receptors, where CNP preferentially binds to type B receptors. Both type A and B receptors are found in the kidneys, vascular smooth muscle, adrenal glands, the heart, and the brain. Natriuretic peptide type A receptors have greater affinity for ANP than for BNP and CNP, respectively. Natriuretic peptide type B receptors have greater affinity for CNP than for ANP and BNP, respectively. Both natriuretic peptide type A and B receptors are part of the extracellular portion of the membrane-bound enzyme particulate guanylyl cyclase. When the receptor is occupied by a natriuretic peptide, the intracellular portion of guanylyl cyclase is stimulated. Guanylyl cyclase generates cyclic guanosine monophosphate from guanosine triphosphate. As the intracellular second messenger, cyclic guanosine monophosphate then stimulates cyclic guanosine monophosphate-dependent protein kinase G (PKG) and cyclic guanosine monophosphate-gated ion channels.

In contrast, natriuretic peptide type C receptors are responsible for natriuretic peptide clearance. Type C receptors have been found in anatomical areas that receive the greatest cardiac output: the renal, pulmonary and cerebral vasculature, adrenals, and the heart chambers. Atrial natriuretic peptide binds more easily to type C receptors than do ANP and BNP, respectively. When occupied by a natriuretic peptide, type C receptors internalize (endocytose), peptide is broken down by hydrolysis, and the receptor returns to the membrane. Natriuretic peptides can also be degraded by circulating neutral endopeptidases. These enzymes hydrolyze the natriuretic peptides and are thought to have a greater role in conditions such as HF, where natriuretic peptide type C receptors may be inundated.

**Natriuretic Peptides and Vasodilatation and Cardiomyocyte Relaxation**

In vascular smooth muscle and contractile heart cells, the natriuretic peptides act through increased levels of cyclic guanosine monophosphate and the resultant changes in intracellular calcium. Smooth muscle relaxation is a direct result of decreased levels of calcium that arises by 4 mechanisms (Figure 9). First, calcium influx into the cell is inhibited by PKG phosphorylation of L-type calcium channels, and the cell is hyperpolarized due to activation of calcium-dependent potassium channels. Hyperpolarization makes smooth muscle cells less prone to stimulation by other vasopressors. Second, calcium efflux is accelerated due to activation of the sodium/potassium ATPase located on the cell membrane and the influence on sodium/calcium exchange. Third, PKG phosphorylation of inositol triphosphate-gated ion channel inhibits the release of calcium stored in the endoplasmic reticulum. Fourth, PKG phosphorylation of phospholamban enhances calcium sequestration via the SERCA on the endoplasmic reticulum. The net result of these mechanisms is decreased calcium available for cross-bridge formation and subsequent vasodilatation. Through these same mechanisms, the natriuretic peptides counteract the effects of the sympathetic nervous system and the effects of ANG II and arginine vasopressin on cardiomyocytes. Particularly in response to chronic HF, natriuretic peptide-induced reduction of intracellular calcium is thought to modulate and ameliorate, at least in part, detrimental cellular and chamber remodeling promoted by other neurohormones.

**Natriuretic Peptides and Diuresis and Natriuresis**

A principal target of the natriuretic peptides in the kidney is the renal arterioles. Vasodilatation of afferent renal arterioles and concomitant vasoconstriction of efferent arterioles lead to
greater glomerular capillary hydrostatic pressure and thereby a greater glomerular filtration rate. Collecting duct cells are also a site of action of natriuretic peptides. In particular, principal cells of the medullary collecting duct have a high proportion of natriuretic peptide type A receptors, which facilitate natriuresis in the following ways. First, cyclic guanosine monophosphate decreases the inward transport of sodium from the lumen of the collecting duct to the medullary interstitium, leaving more sodium in the lumen for elimination. Second, cyclic guanosine monophosphate stimulates PKG, which in turn phosphorylates several proteins, including the same sodium channel on the lumen membrane (also known as apical membrane) of the principal cell affected directly by cyclic guanosine monophosphate, and the sodium potassium ATPase that is located on the peritubular membrane (also known as basolateral membrane) of the principal cells. When receptors are occupied by natriuretic peptides, this sodium potassium ATPase is inhibited, further decreasing sodium reabsorption. The net effects of the actions of the natriuretic peptide-stimulated increase in cyclic guanosine monophosphate are natriuresis and diuresis.

Unlike the majority of the other systems described, endogenous natriuretic peptides are cardioprotective. Cardioprotection by natriuretic peptides may be more effective during simultaneous therapeutic blockade of

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**Figure 9:** Natriuretic peptide type A/B receptor-mediated vasodilatation. Guanylyl cyclase generates cGMP from GTP. In vascular smooth muscle cells, cGMP stimulates PKG, which phosphorylates several targets, ultimately leading to vasodilatation due to (1) decreased calcium influx secondary to PKG phosphorylation of L-type calcium and membrane hyperpolarization due to activation of calcium-dependent potassium channels; (2) acceleration of membrane sodium/potassium ATPase fuels greater sodium/calcium exchange and thereby calcium efflux; (3) inhibition of IP3-gated calcium channels, decreasing intracellular calcium; and (4) PKG phosphorylation of phospholamban accelerates SERCA and calcium resequestration into the endoplasmic reticulum. All actions favor decreased intracellular calcium, smooth muscle relaxation, and vasodilatation.

Abbreviations: ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; NPR, natriuretic peptide receptor; GC, guanylyl cyclase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; PKG, protein kinase G; Ca\(^{2+}\), L-type calcium channel; K\(_{\text{Ca}}\), calcium-dependent potassium channel; Na/K, sodium-potassium-ATPase; Na/Ca, sodium-calcium exchange; PL, phospholamban; Ca\(^{2+}\), calcium; SERCA, sarcoendoplasmic reticulum adenosine triphosphatase; ER, endoplasmic reticulum; IP3-gated Ca\(^{2+}\), inositol triphosphate-gated calcium channel.
other systems such as the sympathetic nervous system, RAAS, and vasopressinergic system.

**Part V: Vasopressinergic System**

**Arginine vasopressin** is a hormone that regulates water balance and cardiovascular homeostasis. Arginine vasopressin is derived from a precursor hormone synthesized in magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus.\(^79,80\) Preprovasopressin is composed of 3 proteins—arginine vasopressin, neurophysin II, and copeptin\(^81\)—and is transported via the supraoptic-hypophyseal tract to the axon terminals of the magnocellular neurons in the posterior pituitary.\(^80\) The active hormone arginine vasopressin is a 9-amino acid protein derived from preprovasopressin\(^80,81\) and is secreted into the circulation from the posterior lobe of the pituitary gland.\(^82\)

**Mechanisms of Arginine Vasopressin Release**

Arginine vasopressin secretion is regulated by both osmotic and nonosmotic mechanisms.\(^79,80,83\) Osmotic secretion is controlled by osmoreceptors sensing changes in sodium concentration. Osmoreceptors located within the hepatic portal vein detect the impact of dietary intake on osmolality, transmitting signals via the vagus nerve to the nucleus tractus solitarius, area postrema, and ventrolateral medulla.\(^84\) Afferent cells from these areas project to the paraventricular nuclei and supraoptic nuclei and depolarize the magnocellular neurons, resulting in increased arginine vasopressin release.\(^79\) Other osmoreceptors are found within the hypothalamus itself and project to the paraventricular and supraoptic nuclei. Arginine vasopressin-secreting magnocellular neurons are also responsive to plasma sodium levels.\(^83,84\)

Nonosmotic arginine vasopressin secretion is particularly important to the study of HF. Baroreceptors in the left atrium, aortic arch, and carotid sinuses transmit afferent impulses to the nucleus tractus solitarius in response to underfilling.\(^79\) High-pressure baroreceptors (located in the aortic arch and carotids) are primarily responsible for initiating nonosmotic arginine vasopressin release.\(^1,40\) Low-pressure baroreceptors also respond to high filling pressures; however, this predominantly leads to sympathetic nervous system activation and natriuretic peptide secretion, not arginine vasopressin release.\(^79\) In healthy humans, increased blood volume that activates low-pressure baroreceptors is a strong signal for the inhibition of arginine vasopressin secretion.

High levels of arginine vasopressin have been detected in patients with HF.\(^82,83\) Hyponatremia, most commonly a menacing sign, is also a common finding in patients hospitalized with HF.\(^79\) It is likely that, in HF, nonosmotic arginine vasopressin secretion is the dominant mechanism of hyponatremia.\(^88\) In HF, distention of left atrial baroreceptors in response to increased central blood volume should inhibit arginine vasopressin expression. Furthermore, both central and peripheral chemoreceptors that detect decreased levels of sodium should also inhibit arginine vasopressin secretion. That is, in HF there is an apparent override of certain nonosmotic and osmotic inhibitory signals to the arginine vasopressin neurons. The exact mechanisms underlying high levels of arginine vasopressin in persons with HF, however, have not yet been described.\(^89\)

**Vasopressin Receptors and Effect of Activation**

Three separate arginine vasopressin receptors have been identified: \(V_{1A}\), \(V_{1B}\) (formally \(V_3\)), and \(V_2\). \(V_{1A}\) receptors are found primarily on vascular smooth muscle cells and cardiomyocytes.\(^80,81\) \(V_{1B}\) receptors primarily exist in the anterior pituitary.\(^90,91\) Both \(V_1\) receptor subtypes are G protein coupled.\(^90\) (For details, see the description of \(\alpha\)-adrenergic receptor activation and Figure 4.) \(V_{1A}\) receptors also modulate ATP-sensitive potassium channels.\(^80\) Adenosine triphosphate-sensitive potassium channels typically promote potassium efflux in conditions of hypoperfusion and inhibit calcium influx, thus inhibiting cells and relaxing smooth muscle. \(V_{1A}\)-receptor activation closes ATP-sensitive potassium channels, enhancing vascular reactivity to arginine vasopressin and other vasoactive substances.\(^80\)

Therefore, activation of \(V_{1A}\) receptors on vascular smooth muscle cells leads to vasoconstriction and increased responsiveness to sympathetic nervous system and other system activation. \(V_2\) receptors on collecting duct cells of the kidneys mediate the antidiuretic properties of arginine vasopressin. \(V_2\) receptors are coupled with a stimulatory G protein and, when activated, stimulate adenylyl cyclase. As described previously, adenylyl cyclase generates cyclic
adenosine monophosphate from ATP. Acting as an intracellular second messenger in renal collecting duct cells, cyclic adenosine monophosphate stimulates protein kinase A, which in turn phosphorylates the aquaporin-2 molecule. When phosphorylated, aquaporin-2 molecules are mobilized to the apical plasma membrane of the collecting ducts and facilitate water reabsorption by forming water channels. Of particular relevance to the patient with HF is the fact that activation of V2 receptors does not result in sodium reabsorption as does aldosterone, leading to the retention of water but not sodium, and predisposing to hyponatremia. Taken together, the vasoconstrictive and water-retaining effects of arginine vasopressin contribute to HF progression rather than compensation.

**Part VI: Endothelin**

Endothelin 1 is a biologically active, 21-amino acid protein that is synthesized by endothelial cells. Although several other endethelins exist within the body, the effects of endothelin 1 have been studied to a greater extent in HF. Because of the potent vasoconstrictive properties of endothelin 1, elevated plasma levels of this protein in patients with HF are of pathophysiologic significance.

**Mechanisms of Endothelin Secretion**

Endothelin 1 is produced within endothelial cells in response to various stimuli, including shear stress, hypoxia, and the presence of other circulating vasoactive hormones such as ANG II and vasopressin. Endothelin 1 is not constitutively expressed; thus, an alteration in endothelial function is required for endothelin 1 secretion. First, the biologically inactive 212-amino acid preproendothelin-1 is cleaved by a furin-like peptide to form another biologically inactive 39-amino acid prohormone called big endothelin. Big endothelin is then cleaved by one of several endethelin converting enzymes to form endothelin 1. Recent evidence suggests that plasma levels of big endothelin and endothelin 1 are superior to the natriuretic peptides in determining survival in patients with HF. Although elevated levels of endothelin 1 have been described in patients with HF, it remains unclear if endothelin 1 expression is increased, or if endothelin 1 degradation is decreased.

**Endothelin Receptors and the Effects of Activation**

Two endothelin receptor subtypes have been identified: endothelin 1 type A receptors and endothelin 1 type B receptors. Both endothelin 1 receptors are Gq-coupled receptors. (For details, see the description of α-adrenergic receptors and Figure 4.) Endothelin 1 type A receptors are found in the vascular smooth muscle cells of the aorta, kidneys, and on cardiac myocytes. Activation of vascular smooth muscle endothelin type A receptors increases intracellular calcium and causes potent and sustained vasoconstriction. Interestingly, the half-life of endothelin 1 is between 1 and 2 minutes, yet the vasoconstrictive effects of endothelin 1 last up to 60 minutes. Activation of cardiomycocyte endothelin 1 type A receptors causes positive chronotropism and inotropism. In right atrial myocytes, type A receptors are also coupled with an inhibitory G protein and inhibit adenylyl cyclase, a phenomenon not found in ventricular myocytes.

Endothelin 1 type B receptors are found predominantly on vascular endothelial cells. Endothelin 1 type B receptors on endothelial cells are also coupled with an inhibitory G protein and promote nitric oxide synthesis. Nitric oxide production from activation of type B receptors on endothelial cells causes vasodilatation by actions on adjacent vascular smooth muscle cells. Type B receptors are also found on vascular smooth muscle cells, but will promote vasoconstriction by identical means as endothelin 1 type A receptors. Thus, the effect of endothelin 1 type B receptor activation is dependent on anatomic location, giving rise to either vasoconstriction or vasodilatation. Vasoconstriction, particularly that which is sustained, further deteriorates cardiovascular function in HF.

**Conclusion**

In this article, mechanisms of activation and cellular and organ system effects of several hormones and mediators in HF have been reviewed. These included the sympathetic nervous system, RAAS, kallikrein-kininogen-kinin system, natriuretic peptide systems, vasopressin, and endothelin. Individually, these systems are complex, and their interactions increase the complexity of pathophysiology and of care for the patient with HF. Understanding mechanisms of compensatory neurohormonal system activation and the
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