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THE ROLE OF NEUROPEPTIDES IN ADVERSE MYOCARDIAL REMODELING AND HEART FAILURE

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Abstract

In addition to traditional neurotransmitters of the sympathetic and parasympathetic nervous systems, the heart also contains numerous neuropeptides. These neuropeptides not only modulate the effects of neurotransmitters, but also have independent effects on cardiac function. While in most cases the physiological actions of these neuropeptides are well defined, what is less appreciated are their contributions to cardiac pathology. Some neuropeptides are cardioprotective, some promote adverse cardiac remodeling and heart failure, and for others their functions are unclear. Some have both cardioprotective and adverse effects depending on the specific cardiac pathology and progression of that pathology. In this review, we briefly describe the actions of several neuropeptides on normal cardiac physiology, before describing in more detail their role in adverse cardiac remodeling and heart failure. It is our goal to bring more focus towards understanding the contribution of neuropeptides to the pathogenesis of heart failure, and to consider them as potential therapeutic targets.

Keywords

Cardiac remodeling; hypertrophy; fibrosis; cardiomegaly

1.0 INTRODUCTION

Nervous system innervation of the heart is traditionally considered to consist of adrenergic (sympathetic) and cholinergic (parasympathetic) inputs that function to increase and decrease both heart rate and force of contraction. However, the heart also contains a wide array of neuropeptides that under physiological conditions modulate traditional sympathetic and parasympathetic signals to the heart. These neuropeptides may originate from parasympathetic, sympathetic, or sensory nerves in the heart [1] and examples include calcitonin gene-related peptide (CGRP), substance P (SP), vasoactive intestinal peptide

(VIP), neuropeptide Y (NPY), as well as a number of others. These neuropeptides are often co-stored and co-released with neurotransmitters. For example, VIP is thought to be a co-transmitter with acetylcholine in intra-cardiac parasympathetic neurons, while neurotensin (NT) and NPY appear to be co-stored with NE in sympathetic nerves. CGRP and SP are co-stored in primary sensory afferent nerves. While the role of these individual neuropeptides in cardiac physiology is well defined, what is not fully appreciated is the critical contribution of many of these neuropeptides to adverse myocardial remodeling and heart failure. In some cases, these neuropeptides act to promote adverse cardiac remodeling, however, in other cases they act to protect or limit the remodeling response. For other neuropeptides, their contribution, if any, is not yet well defined. These effects on remodeling involve direct actions on cardiac cells as well as cross-talk between sympathetic, parasympathetic, and sensory nerves [1]. This review will briefly describe the actions of several neuropeptides on cardiac physiology, but will focus on what is known about their role in adverse cardiac remodeling and heart failure. With this review, we hope to bring more attention towards understanding the contribution of neuropeptides to heart failure, and to consider them as potential therapeutic targets.

2.0 CALCITONIN GENE-RELATED PEPTIDE (CGRP)

2.1 Localization and Physiological Actions in the Heart

Probably the most studied neuropeptide in adverse cardiac remodeling and heart failure is CGRP. CGRP is a 37 amino acid peptide (Table 1), primarily localized to C and A δ sensory nerve fibers, which is also a common location of SP (see section 3.0) [2]. There are two major isoforms of CGRP (α CGRP and β CGRP) that are derived from alternate splicing of the *Calc1* and *Calc2* genes respectively [3, 4]. Both isoforms share more than 90% homology with only three amino acids difference, suggesting similarities in their biological activities [5, 6]. α CGRP is mainly found in the central and peripheral nervous system whereas β CGRP is primarily found in the enteric nervous system [7, 8]. The receptor for CGRP is made up of two different subunits, namely the calcitonin receptor-like subunit (CRL) and receptor activity modifying protein (RAMP). There are three RAMP isotypes, RAMP1, RAMP2 and RAMP3 [9, 10]. Heterodimerization between CRL and RAMP1 has a high affinity for CGRP (Table 1), while the heterodimerization between CRL and RAMP2 and CRL and RAMP3 are recognized as adrenomedullin 1 and adrenomedullin 2 receptors, respectively [11, 12]. In order for the CGRP receptor to be fully functional, a small (~17kDa) hydrophilic membrane associated protein called receptor component protein is required [13].

CGRP containing nerve fibers are present in the heart, particularly around the coronary arteries, papillary muscle and in the excitatory regions such as the sinoatrial and atrioventricular nodes [8]. CGRP is a potent vasodilator, particularly of the coronary vasculature. This is predominantly mediated by nitric oxide-related mechanisms. In fact, CGRP is the most potent microvascular dilator known [14]. Exogenous CGRP exerts positive inotropic and chronotropic responses on the heart. This is likely a response to the CGRP-mediated reduction in systemic blood pressure and occurs via direct actions on cardiomyocytes as well as reflex sympathetic nervous system activity [14, 15].

2.2 Cardioprotective Actions of CGRP

CGRP has been shown to play a cardioprotective role in heart failure. Infusion of exogenous CGRP in heart failure patients improves myocardial contractility [16, 17], as well as reducing peripheral resistance [17]. Using a model of a transverse aortic constriction, Li et al., [18] showed that wild type (WT) mice had elevated myocardial levels of CGRP. Interestingly, this increase was not sustained at 21 days post transverse aortic constriction, which mimics the increase in CGRP levels during early heart failure in humans that then declines in the later stages [18, 19]. In comparison to WT mice with aortic constriction, $\alpha\text{CGRP}^{-/-}$ mice had worsened left ventricular (LV) hypertrophy, perivascular and interstitial fibrosis, and mortality. Moreover, CGRP was shown to be protective against inflammation including macrophage infiltration and TNF- α production [18]. CGRP was also shown to protect against cell death since the $\alpha\text{CGRP}^{-/-}$ mice exhibited an increased number of apoptotic cells, clear cardiomyocyte necrosis, as well as angiogenesis inhibition in comparison to their WT counterparts [18]. The anti-apoptotic effects of CGRP are strengthened by a later study in which pretreatment of isoprenaline-treated rat cardiomyocytes with CGRP inhibited apoptosis and reactive oxygen species (ROS) production; a CGRP receptor antagonist abrogated this effect [20]. Following acute myocardial infarction (MI), CGRP levels in plasma and nerves increases in humans as a response to the metabolic stress and decreased vasodilation that occurs after ischemia [21, 22]. Consistent with this, the $\alpha\text{CGRP}^{-/-}$ mouse is more susceptible to the effects of ischemia/reperfusion injury, as shown by an increase in vascular cell damage and increased malonaldehyde levels, an indicator of ROS production. In addition, recovery after the injury was stunted, possibility due to the loss in CGRP induced vasodilation [23].

Extensive studies have been conducted on rutaecarpine, a compound extracted from the *Erodia rutaecarpa* plant, which is a transient receptor potential vanilloid 1 (TRPV1) agonist and induces the release of CGRP. In a isoprenaline model of heart failure in the rat (5 mg/kg body weight for 10 days), rutaecarpine (10 or 40 mg/kg) induced CGRP release and was shown to be protective against cardiac hypertrophy, collagen deposition and apoptosis [24]. Rutaecarpine (10, 20 or 40 mg/kg per day) twice daily for 18 days, induced a hypotensive effect in spontaneously hypertensive rats (SHR) concomitant with increased levels of CGRP. In addition, rutaecarpine also inhibited platelet aggregation by decreasing the level of tissue factor in the plasma. Interestingly, exogenous CGRP exerted the same effect on platelet aggregation and decreased platelet derived tissue factor *in vitro*.

Overall, CGRP has been well established as an important cardioprotective neuropeptide. It improves coronary circulation and opposes cardiomyocyte death and hypertrophy, as well as being anti-fibrotic.

3.0 SUBSTANCE P (SP)

3.1 Localization and Physiological Actions in the Heart

In recent years there has been an increased interest in the contribution of SP to cardiac remodeling and heart failure. SP an 11 amino acid member of the tachykinin family of neuropeptides (Table 1) and was first discovered and extracted from equine brain and

intestine in 1931 by Van Euler and Gaddum [25]. SP is derived from the *Tac1* gene that also encodes neurokinin A (NKA, see Section 10.0), neuropeptide K and neuropeptide- γ [26]. The human *Tac1* gene consists of seven exons and its transcription generates pre-mRNA that can be alternatively spliced, resulting in four different mRNA isoforms: α , β , γ , δ . All four isoforms give rise to SP whereas only the β and γ isoforms give rise to NKA. Hence SP can be produced without NKA, however the NKA will always be accompanied by the production of SP [27, 28]. The distribution of SP in the heart does show some small variations between species, however, overall SP is mainly confined to C-fiber sensory nerves that innervate the coronary arterial system, the intrinsic cardiac neural plexus, intrinsic nerve bundles, and interganglionic nerves in the atria, and occasionally cardiomyocytes [29–34]. A small population of coronary endothelial cells have been reported to produce SP [35].

The biological actions of tachykinins are mediated by neurokinin receptors, which are part of the rhodopsin like G protein receptor family [36]. There are three neurokinin receptors that have been identified, the neurokinin 1 (NK-1R), neurokinin 2 (NK-2R), and neurokinin 3 receptor (NK-3R). SP preferentially binds to the NK-1R (Table 1), whereas NKA and neurokinin B (NKB) have greater affinity for the NK-2R and NK-3R respectively. NK-1Rs can also mediate the actions of NKA and NKB, although SP has a significantly greater affinity over NKA and NKB (~100 and 500 times, respectively) [37]. The NK-1R occurs as two isoforms. The full length receptor consists of 406 amino acids, while the truncated receptor lacks the final 96 amino acids of the intracellular C-terminus tail [26, 38]. The truncated isoform has 10 times lower affinity for SP than the full length isoform. In addition, it does not undergo rapid desensitization and internalization [39], presumably meaning that it exerts prolonged effects. The truncated isoform is most prevalent in peripheral tissues including the heart [40], possibly making it relevant in heart failure.

Consistent with its localization, SP is a potent coronary vasodilator, with this action being nitric oxide mediated [41]. Also consistent with its localization, SP regulates heart rate and force of contraction [41]. SP induces bradycardia, which subsequently leads to an increase in force of contraction presumably to maintain cardiac output.

3.2 Acute Cardioprotective Actions of SP

Rat hearts depleted of sensory nerve neuropeptides by capsaicin, and subjected to global ischemia reperfusion showed reduced heart rate recovery, coronary flow, and LV developed pressure in comparison to the control group. The addition of SP restored contractile function and coronary flow [42]. Since that finding, a variety of studies using ischemia reperfusion as well as pre- and post-conditioning protocols have described a cardioprotective role for SP in the heart [42–45]. Notably, Wang et al., [43] demonstrated in isolated mouse hearts undergoing ischemia reperfusion, that blocking the NK-1R caused LV end diastolic pressure (EDP) to increase and contractile function to decrease, indicating that endogenous SP provided a degree of protection from ischemic damage. The addition of exogenous SP reduced LVEDP and improved contractile function, indicating that exogenous SP provides additional protective effects beyond those provided by endogenous SP. The cardioprotective role of SP has mainly been attributed to its potent coronary vasodilator properties. However, we recently identified that adult mouse cardiomyocytes possess the NK-1R, and using

isolated rat hearts and a novel rat LV slice culture system, we found that SP protects against ischemia-related cell death by direct activation of AKT survival pathways [46]. In other words, the effects were independent of vasodilation. It is important to emphasize that all of the studies that have shown protective actions of SP in the ischemic heart have been acute ex vivo studies. What is not known is the long-term effect of SP in the ischemic heart. This is especially complicated given the findings described in the following section of this article indicating that SP is detrimental in chronic (although non-ischemic) cardiac remodeling. Thus, we hypothesize that SP is protective in the infarcted region acutely, but promotes adverse remodeling in the remote LV chronically. This is yet to be established, however, a recent clinical study has identified that patients with higher plasma levels of the pro-form of SP following MI, have a greater risk of heart failure or mortality within two years [47].

Two interesting aspects of SP biology that have received very little attention are its contributions to diabetic cardiomyopathy and atrial fibrillation. SP and the NK-1R are decreased in atrial biopsies from diabetic patients [48], and Ren et al., [45] reported that while SP levels were increased in normal rat hearts exposed to a global post-conditioning ischemia reperfusion model, SP did not increase in diabetic hearts. Post-conditioning protection could be restored by exogenous SP. Thus, a loss of SP brought on by diabetes could predispose the heart to excessive injury in the event of a MI, in keeping with the protective role of SP in this setting. However, again these were acute studies using isolated heart approaches, thus, the long term in vivo role of SP in the diabetic heart is unknown. A loss of cardiac SP may also predispose the heart to atrial fibrillation. Yu et al., [49] paced dog hearts (600 beats/minute) to induce atrial fibrillation and found that although there was an increase in sympathetic nerve fibers in the atria, there was a dramatic loss of SP-containing nerve fibers. Guler et al., [50] reported that plasma levels of SP significantly decreased in patients two days after coronary artery bypass surgery. This reduction was greater in patients that suffered post-operative atrial fibrillation, although it is not clear whether this decrease in SP was significantly different to non-atrial fibrillation patients. Given that most cardiac SP is located in the atria and that SP can affect heart rate (bradycardic), it makes sense that a loss of SP could contribute to atrial fibrillation.

3.3 Chronic Adverse Effects of SP

SP plays a detrimental role in non-ischemic myocardial remodeling and heart failure. William Weglicki's group was instrumental in identifying a role for SP and adverse cardiac remodeling. Using a model of magnesium deficiency in rats and mice, they showed that SP levels increase and that blockade of the NK-1R significantly decreased levels of pro-inflammatory cytokines such as TNF α and IL-1, as well as improving diastolic and systolic function [51–53]. In myocarditis, SP levels have been shown to be elevated by 40–60 fold [54, 55]. Mice deficient in SP had reduced mortality as well as reduced LV hypertrophy, inflammation and necrosis in this model. In a model of chronic volume overload induced heart failure, our laboratory determined that deletion of the gene for SP (*Tac1*) in mice, protects them from developing LV hypertrophy (ventricular dilation). The underlying mechanisms included prevention of MMP activation and collagen degradation by deletion of *Tac1* [56]. More recently, we reported that blockade of the NK-1R prevents cardiac fibrosis in the SHR heart, independent of blood pressure [57]. Interestingly though, while SP does

induce cardiac fibroblast proliferation [58], it does not cause cardiac fibroblasts to convert to myofibroblasts or produce excess amounts of extracellular matrix [57–59]. However, cardiac fibroblasts do possess the NK-1R and do up-regulate key extracellular matrix-related as well as cell adhesion genes, suggesting that SP may ‘prime’ fibroblasts for a response to other stimuli [57, 59, 60]. Thus, indirect mechanisms likely play a role in mediating the fibrotic actions of SP. To this end, we reported that NK-1R blockade prevented the increase in endothelin-1 (ET-1) levels observed in the hypertensive rat heart [57], indicating that ET-1 may be an indirect mechanism by which SP promotes cardiac fibrosis. In addition to the pro-fibrotic actions of SP, NK-1R blockade also prevented induction of fetal genes in the SHR heart, confirming in the adult heart the original findings of Church et al., [61] that SP could induce atrial natriuretic factor production by neonatal rat cardiomyocytes.

3.4 SP and Chemotherapy-Induced Cardiotoxicity

Two recent studies have investigated a possible role for SP in chemotherapy-induced cardiotoxicity. Tyrosine kinase inhibitors such as erlotinib can induce cardiotoxicity, involving inflammation and oxidative stress [62]. Of note, SP levels are increased by erlotinib in rats [63]. NK-1R blockade with aprepitant reduced oxidative stress, reduced LV wall thinning, and returned cardiac function to normal (as determined by ejection fraction). The anthracycline, doxorubicin, also induces a cardiotoxicity involving cardiomyocyte apoptosis and cardiac fibrosis that ultimately leads to a dilated cardiomyopathy and heart failure [64]. Robinson et al., [65] recently used the H9c2 cardiomyocyte-like cell line to examine the role of the NK-1R in doxorubicin-induced cell death. Aprepitant reduced apoptotic cell death in H9c2 cells exposed to doxorubicin. Doxorubicin dramatically increased levels of reactive oxygen species produced by H9c2 cells, and this was greatly attenuated by aprepitant, providing a possible mechanism underlying the effects on apoptosis. Of interest, this study found that H9c2 cells produced SP in response to doxorubicin, raising the possibility that cardiomyocytes could be a source of SP in the diseased heart.

Overall, the effects of SP and the NK-1R on remodeling are complex. SP is cardioprotective acutely in the setting of ischemia reperfusion. Conversely, SP promotes adverse cardiac remodeling chronically. The NK-1R receptor is an exciting potential therapeutic target since there two commercially available and clinically used NK-1R antagonists; aprepitant (Emend, MK-869, L-574,030) and its intravenously administered prodrug, fosaprepitant (Ivemend, MK-0517, L-758,298) [41]. These drugs are approved as antiemetics for vomiting in cancer patients undergoing chemotherapy, and also used to prevent nausea and vomiting in post-surgery patients [66]. This is also interesting given the possible role of SP and the NK-1R in chemotherapy-induced cardiotoxicity.

4.0 SOMATOSTATIN (SS)

4.1 Localization and Physiological Actions in the Heart

SS is a 14-amino acid cyclic peptide (Table 1), known predominantly for its inhibitory effect on the actions of growth hormone, however, it also has effects on the cardiovascular system. In the *Bufo marinus* (Cane Toad) heart, SS is localized in the nerve fibers within muscle

bundles of both the atria and ventricles, especially through the vagal inhibitory routes [67]. SS is found in abundance in the atria and the atrioventricular node [68]. Five receptor subtypes have been identified for SS (sst1 to 5). Both the atria and ventricles show expression for four of these receptors (Table 1), with sst3 being the only receptor not present. While cardiac fibroblasts express the four receptor types, cardiomyocytes are known to express only sst1 and 2 [69], thus, SS may exert different effects on cardiomyocytes and cardiac fibroblasts.

SS is a negative inotrope, possibly due to decreasing the inward Ca^{2+} current [70] or the inwardly rectifying K^{+} channel [71], behaving similarly to acetylcholine [72]. Intracerebroventricular administration of SS resulted in dose-dependent increases in mean arterial blood pressure in conscious rats, likely due to its effect on increasing the levels of vasopressin, but still decreasing heart rate [73]. However, such effects were not observed when SS was given intravenously, showing the involvement of central nervous system and vasopressin in the cardiovascular effects of SS [74]. However, the role of SS in the normal heart is not entirely clear since in contrast to the studies showing the negative inotropic effects of SS, one study showed a positive inotropic effect in the guinea pig ventricular muscles, also possibly due to effects on the inward Ca^{2+} current [75]. Also, infusion of the SS analogue, SMS 201–995, did not show any significant changes in LV function, heart rate, or blood pressure in healthy individuals [76].

4.2 Cardioprotective Effects of SS

SS analogues inhibit insulin-like growth factor (IGF)-1 and basic fibroblast growth factor (bFGF)-stimulated proliferation of human coronary artery vascular smooth muscle cells (VSMCs) *in vitro*, although not affecting VSMC migration [77]. In the heart, four weeks of injections of the SS analogue, octreotide (50–100 micrograms), in patients with primary hypertrophic cardiomyopathy, were shown to be beneficial, due to the inhibition of growth factors [78]. The positive outcomes in cardiac parameters in these patients were broad, including a reduction in the thickness of posterior wall and interventricular septum, reduced LV mass, as well as an increase in the end systolic and end diastolic LV diameters [78]. In a similar study involving 15 patients with hypertrophic obstructive cardiomyopathy, treatment with octreotide for 6 months improved LV septum and wall thicknesses as well as the sub-aortic pressure gradient [79]. In the rat heart, the stable SS analogue, angiopeptin, inhibited IL-1 β induced adhesiveness of endothelial cells to mononuclear cells [80]. SS was also shown to be effective in restoring sinus rhythm by treating re-entry tachycardia in six of seven patients [81]. The most widely reported improvements in cardiac structure and function with SS or its analogues appears to be in cardiovascular disease that is secondary to abnormal levels of growth hormone, especially in acromegaly [82–85], likely due to its ability to reduce secretion of growth promoting hormones. Eleven patients with acromegaly showed improvements in cardiac mass and function as measured by echocardiography after 6-months of treatment with octreotide [82]. Similarly, cardiac magnetic resonance imaging showed reduced LV hypertrophy following six months of treatment with another SS analogue, lanreotide, in 14 patients with acromegaly [83]. Improvements in cardiac fibrosis as well as systolic function were shown in 22 patients with acromegaly, after treatment with the SS analogue, sandostatin, for six months [84]. Finally, heart rate variability in

acromegaly patients in the form of increased arrhythmias, as well as its control after treatment with various SS analogues, was reported through 24hr ECG measurements in 28 patients [85].

4.3 Adverse Cardiac Remodeling

An SS-like cyclic peptide, urotensin II (UII), has been shown to negatively affect the cardiovascular system through effects on the heart [86] as well as endothelium-independent vasoconstriction [87]. UII has high structural similarity to SS and binds to SS receptors [88]. Ames et al., [89] demonstrated cardiovascular collapse in cynomolgus monkeys after injecting UII. Furthermore, studies have shown increased levels of this peptide in patients with congestive heart failure [86, 90], as well as rats with MI [91] and right ventricular hypertrophy [92]. An upregulation of UII and its receptor protein was shown within the myocardium of diabetic rats [93], as well as in a rat model of heart failure post-MI [91]. Increased collagen synthesis by cardiac fibroblasts has also been observed *in vitro* with UII [91]. While hypertrophy was not present at the cellular level, an increased activation of UII-dependent hypertrophic signaling was evident during the expression of recombinant UII receptors in neonatal rat cardiomyocytes [91]. Given the high potency of UII (generally agreed to be the most potent endogenous vasoconstrictor identified) and its wide receptor locations in the cardiovascular system, as well as other systems including renal, its roles in cardiovascular, renal, and metabolic disorders cannot be underestimated [94].

5.0 VASOACTIVE INTESTINAL PEPTIDE (VIP)

5.1 Localization and Physiological Actions in the Heart

VIP is a 28 amino acid neuropeptide discovered by Said and Mutt in 1970 (Table 1). The amino acid sequence is highly conserved with human, bovine, sheep, goat, dog, rabbit, and rat VIP being identical, and guinea pig and non-mammalian VIP differing by four or five amino acids [95]. VIP is generated from cleavage of the precursor molecule preproVIP. Coronary vessels are supplied by VIP-containing nerve fibers [96], with the coronary arterial system typically containing more VIP-containing nerve fibers than the venous system. There is an increased association of VIP fibers with the vasculature around the sinoatrial and atrioventricular nodes. Non-vascular VIP-containing fibers are also prominent in the sinoatrial node, atrioventricular node and Purkinje-fibers [96]. In the ventricles, VIP is found almost exclusively in nerve fibers projecting to the coronary vasculature and is rarely found projecting to ventricular myocytes. There are two known VIP receptors, VPAC1 and VPAC2 [95]. Both receptors are found in the heart (Table 1) and are coupled to adenylyl cyclase and cyclic AMP [95, 97]. Macrophages account for VPAC1 receptors in the normal ventricle, while VPAC2 receptors are mainly found on smooth muscle cells, but also on occasional cardiomyocytes [97].

In terms of cardiac physiology, VIP increased heart rate in dogs, however, this response was of slower onset than to norepinephrine (NE) [98]. However, VIP is more potent than NE. Similarly, VIP induced a positive inotropic response in trabeculae muscle isolated from both atria and ventricle of dogs [99]. Interestingly, VIP was 9-fold and 3-fold more potent than isoproterenol in eliciting an increased inotropic response in atrial and ventricular trabeculae,

respectively. VIP also induces coronary artery vasodilation via VPAC2 receptors. This appears to involve K_{ATP} channels, but not K_V channels [100]. Activation of PKA and subsequent phosphorylation of phospholamban, leading to increased sequestration of Ca^{2+} in the sarcoplasmic reticulum of smooth muscle cells may also contribute [95]. In the sinoatrial node, VIP-induced PKA activation accelerates the rate of diastolic depolarization to increase heart rate [95]. In ventricular cardiomyocytes, VIP causes an increase in cyclic AMP-induced PKA activity, which in turn results in Ca^{2+} release from the sarcoplasmic reticulum and increased rate and force of contraction [95]. VIP-induced PKA activation can also increase phospholamban phosphorylation and increased uptake of Ca^{2+} , resulting in increased ventricular relaxation.

5.2 VIP in Heart Failure

VIP was not increased in patients with congestive heart failure [101], was slightly elevated in patients with heart failure due to aortic stenosis (22.6 ± 0.9 vs 21.1 ± 0.5 pmol/L) [102], and was significantly increased in patients with dilated cardiomyopathy [103]. Interestingly, plasma VIP was inversely related to New York Heart Association (NYHA) class [103]. VIP mRNA increases significantly in the stellate ganglion during the first week of ischemia reperfusion in mice [104]. These inconsistent findings may reflect the stage of heart failure or etiology, however, they provide little insight into the possible role of VIP in the remodeled heart. However, Kalfin et al. [105] used an isolated perfused rat heart preparation to investigate the effect of exogenous VIP on cardiac function following ischemia reperfusion. Isolated hearts were pretreated with VIP (0.1, 0.3, and 1.0 μ M) before initiating 30 minutes of global ischemia followed by 60 minutes reperfusion. VIP levels continually increased over the 60 minutes reperfusion period indicating endogenous VIP release in response to reperfusion. Interestingly, the addition of exogenous VIP dose-dependently increased LV developed pressure and dp/dt before ischemia, which continued during the reperfusion period, albeit at a reduced level. This corresponded with an increased coronary flow. Interestingly, VIP reduced the increased Ca^{2+} transients observed after ischemia reperfusion. This study did not investigate the role of endogenous VIP, however, these findings obtained with exogenous VIP strongly suggest a protective role for this neuropeptide, at least in ischemia reperfusion injury. In the STZ model of diabetes, VIP in the atria decreases significantly following 16 weeks of diabetes [97]. VPAC2 decreased initially then increased in the atria over this time. In the ventricles, VIP levels were decreased by 16 weeks. Interestingly, VPAC2 levels increased in both ventricles at 8 weeks post-STZ, before returning to normal by 16 weeks. The loss of VIP in the diabetic heart again suggests a possible protective role for VIP [105]. Somewhat in support of a protective role for VIP, mice deficient in VIP develop a thinning of the wall of the LV [106]. Several genes associated with cardiomyopathy were up-regulated in the hearts of VIP^{-/-} mice including TNF- α , calsequestrin 1, Titin, Nuclear Factor of Activated T cells (Nfatc3) amongst others. However, it is important to note that mice were studied as a single group containing animals from 9 to 52 weeks of age. Although no significant reduction in LV ejection fraction was noted in these mice, a follow-up study found that mortality in the VIP^{-/-} mice began at 5 months of age, with 50% mortality by 7 months of age [107]. No VIP^{-/-} mice survived to 20 months of age. The authors also reported a progressive right ventricular hypertrophy in relation to the LV. This was not identified in the authors' previous article

[106], and given the LV wall thinning that was reported in that article without changes in chamber size, the right ventricular hypertrophy may reflect a reduction in LV weight rather than an increase in right ventricular weight. Due to its systemic vasodilatory properties, VIP may be useful in treating vascular remodeling that often accompanies heart failure [108]. This would be particularly true in heart failure with preserved ejection fraction. Of note, VIP was found not to be involved in the phenomenon of resistance to ventricular arrhythmias that occurs in response to stimulation of the vagal nerve [109].

6.0 NEUROTENSIN (NT)

6.1 Localization and Physiological Actions in the Heart

NT is a 13 amino acid peptide (Table 1) originally extracted from the bovine hypothalamus [110]. NT has been identified in all four chambers of the rat heart, with the left atrium having the greatest amount, followed by the right atrium, the right ventricle, and then the LV [111, 112]. The two ventricles have dramatically lower levels than the two atria, likely due to the higher preponderance of NT-containing nerve fibers in the atria. In guinea pigs, NT-containing nerve fibers and varicosities are found in high numbers in the sinoatrial and atrioventricular nodes, including nodal cells and blood vessels [113]. Cardiac ganglia also contain NT-positive nerve fibers. In the ventricles, NT nerve fibers are associated with the left and right coronary arteries and the downstream branches, as well as arterioles and capillaries. NT nerve fibers are more numerous than those containing SP in all regions of the heart, and NT and SP are contained in separate nerve fibers [113].

There are three known NT receptors, NTS₁, NTS₂, and NTS₃ [110] (Table 1). NTS₁ and NTS₂ are 7 transmembrane spanning G-protein coupled receptors, with NTS₁ being the high affinity receptor and NTS₂ the low affinity receptor. NTS₁ is expressed in rat cardiac tissue, while NTS₂ is expressed in rat and human, but not mouse cardiac tissue [110]. The NTS₃ receptor is an intracellular binding site expressed in human, rat, and mouse cardiac tissue, but not thought to mediate the major effects of NT on the heart. This is thought to be the role of NTS₁ [110], although mRNA levels for NTS₂ have been observed to increase in response to leukemia inhibitory factor in isolated neonatal rat cardiomyocytes [114].

Cardiac physiological responses to NT show substantial species differences. NT induces coronary vessel constriction in the perfused rat heart, increasing coronary perfusion pressure [115, 116]. Conversely, NT produces coronary vasodilation in guinea pig hearts, at least in part mediated by acetylcholine [117]. In intact dogs, NT increased coronary blood flow, indicative of vasodilation, when administered at normal coronary perfusion pressures [118]. From a cardiac function standpoint, NT has been shown to induce positive inotropic and chronotropic responses in both guinea pig and rat auricles [119], as well as isolated-perfused guinea pig hearts [120]. In fact, NT was more potent than epinephrine in its actions on the auricles [119]. NT exerts powerful inotropic responses in the paced isolated perfused rat heart under conditions of constant flow, being equally as effective as NE, and more effective than histamine, serotonin, and angiotensin II in promoting increased force of contraction [112]. The inotropic effects of NT involve β 1-adrenergic receptors. However, species differences exist when it comes to contractile responses as well, with rabbit auricles and dog hearts not responding to NT [98, 119].

6.2 NT in Heart Failure

Whether or not NT has a role in the development of heart failure is unclear. NT has been observed to decrease in all four chambers in a rat model of monocrotaline-induced right-sided hypertrophy and heart failure [111]. However, the significance of this is unknown. Conversely, a cohort of patients (average age of 64.5 yrs – range 48–76 yrs) with congestive heart failure (NYHA class II and III - mean ejection fraction of $23.7 \pm 2.3\%$) tended to have increased plasma levels of NT [101], although this did not reach statistical significance, likely due to the low number of patients.

Interestingly, the ability of NT to elicit NE release from the heart disappears in isolated hearts from rats receiving chronic isoproterenol (0.05 mg/kg daily for 1 month) [121], a situation mimicking chronic catecholamine release in heart failure. The NT-induced increase in contractile function (developed pressure) in isolated rat hearts was also significantly blunted in isoproterenol pre-treated hearts [121]. The reduced effectiveness of NT in hearts exposed to prior β -receptor activation is indicative of the reduced ability of NT to cause NE release in hearts chronically exposed to β -receptor activation, and may also be due to the downregulation of β -receptors that occurs in heart failure. Together these findings suggest that NT may be ineffective in the stressed myocardium where adrenergic desensitization has occurred. The authors of this study concluded that down-regulation of NT-induced NE release in the diseased heart may be an important effect to protect the heart against further β -receptor-mediated apoptosis, necrosis, extracellular matrix remodeling, and pump dysfunction [121]. Interestingly though, in another study from the same group, NE release in response to NT was greater from hearts isolated from SHR than the normotensive WKY control [122]. Further, NT increased contractility in the SHR [122]. These effects were prevented by β -blockade showing that these effects were also mediated by NE. The interactions between NT and the adrenergic system may be dependent on NE levels and also levels of the β -adrenergic receptors.

There is evidence in rat isolated hearts that NT can induce mast cell activation [123]. This provides the potential for NT to promote adverse myocardial remodeling since mast cells have been shown to play a role in this process in numerous etiologies [124–132]. As an aside, mast cell products do not appear to be the mechanism of NT-induced coronary vasoconstriction [123]. Nor is mast cell histamine a mechanism of NT-induced tachycardia [120]. Further to the argument that NT may be causative in adverse cardiac remodeling, the human fetal lung fibroblast line (IMR90) showed increased proliferative capabilities when treated with insulin and NT over and above the effects of insulin alone [133]. NT alone had no effect on fibroblast proliferation. These data suggest that NT could play a role in fibrosis in the heart that occurs in the setting of diabetes. Of note, in a prospective study of 4632 patients, fasting plasma pro-NT was found to be associated with diabetes, cardiovascular disease, total mortality, breast cancer, and cardiovascular mortality in women [134]. This relationship was not present in men.

7.0 NEUROPEPTIDE Y (NPY)

7.1 Localization and Physiological Actions in the Heart

NPY is a 36 amino acid neuropeptide (Table 1) and part of a family of peptides that includes peptide YY and pancreatic polypeptide [135]. NPY exerts its actions through five known receptors (Y_1 to Y_5). NPY is the most abundant neuropeptide in the heart and the main NPY receptors in the heart are Y_1 , Y_2 , and Y_5 , with Y_5 being the most abundant NPY receptor in cardiomyocytes [135–138] (Table 1). Interestingly, NPY may also be able to activate GTPases in the heart in a receptor-independent manner [139]. In the heart, NPY is found in the intracardiac ganglia, sympathetic nerves projecting to blood vessels, the endocardium, intrinsic parasympathetic cardiac neurons, and even cardiomyocytes [135]. In the rat, rabbit, and guinea pig, NPY immunoreactivity is greater in the left atrium than in the right [140]. However, human autopsy samples showed similar amounts across both atria. In the ventricles, more NPY is found in the right ventricle than in the left [140]. NPY is more abundant in the atria than ventricles. Physiologically, NPY is a potent constrictor of coronary arteries via direct actions on vascular smooth muscle cells [135]. NPY and NE are usually co-released in the heart under conditions of sympathetic nerve activation [141], and in many instances NPY works synergistically with NE since NPY increase cardiomyocyte contractility. Isolated rat ventricular cardiomyocytes responded to NPY (100 nM) by increasing the calcium transient and increasing cell shortening, indicative of increased contraction [142]. Calcium transient decay was also increased by NPY, indicating increased cell relaxation. Interestingly, the authors found that the Y_1 receptor mediated the increased calcium transient via a mechanism involving PLC, however, both Y_1 and Y_2 participated in the increased calcium re-uptake induced by NPY. However, in contrast to NE, there is evidence that NPY can reduce cardiomyocyte contractility [99, 143], and also isoproterenol-induced increased cardiomyocyte contractility [136, 143]. Thus, under some conditions NPY may increase the inotropic response of cardiomyocytes, and in other cases may reduce the inotropic response. NPY also has the effect of mediating cross talk between the sympathetic nervous system and the vagus nerve. Using a spontaneously beating sinoatrial node/right vagal nerve preparation, Herring et al. [144] found that NPY could reduce the bradycardia induced by stimulation of the vagal nerve. This effect involved preventing the release of acetylcholine from the vagal nerve by a mechanism involving Y_2 receptor activation of PKC in cholinergic neurons innervating the SA node.

7.2 NPY in Heart Failure

NPY mRNA decreases significantly in the stellate ganglion over the first week following ischemia reperfusion in mice [104]. However, enlargement of the stellate ganglia occurs by five weeks post-MI in Yorkshire pigs [145] in both the left and right stellate ganglia regardless of which ventricle is infarcted, and there is a significant increase in the number of neurons in both the left and right stellate ganglia that label positive for NPY. In humans, plasma NPY tended to be increased in patients with congestive heart failure, but did not reach statistical significance [101]. However, several studies have shown robust increases. Ullman et al. [146] found increased plasma NPY levels in acute-MI patients. In another study, NPY levels were significantly increased in heart failure patients (366 ± 28 ng/L vs. 89 ± 22 ng/L) and were associated with severity of heart failure [147]. Further, patients that

improved in response to heart failure therapy had reduced NPY plasma levels. In fact, NPY was a prognostic indicator of mortality in non-acute MI patients [148]. In patients with ST elevation MI (STEMI), plasma NPY levels decrease upon reperfusion therapy, although still remaining above normal [149]. NPY levels were higher in patients with no-reflow versus those where reperfusion was successful. Interestingly, Clarke et al [150] demonstrated that infusion of picomolar amounts of NPY into human coronary arteries can induce small vessel constriction and ischemia, which may explain why patients with NPY levels that remained high still had no-reflow upon reperfusion therapy. Interestingly, in a cohort of congestive heart failure patients, plasma NPY were elevated along with NE levels, however, only NE levels increased in response to exercise [151]. It is important to recognize that in all of these patient studies, NPY levels are circulating levels, and interestingly, plasma NPY levels increased in a rat model of cardiac volume overload [137], however, atrial and ventricular NPY levels decreased, especially in rats where the hearts had decompensated. Thus, there may be discrepancies in local tissue production versus systemic release of NPY and, therefore, possibly different systemic versus tissue actions. Interestingly, Y_1 receptor mRNA also decreased in both compensated and decompensated volume overload hearts, whereas Y_2 receptor mRNA increased in compensated hearts and further increased in decompensated hearts [137]. This may also represent a shift in which receptor mediates the actions of NPY in the diseased heart and may indicate a change in function.

Probably not surprisingly, NPY serum levels were observed to be increased in a patient case study with stress-induced cardiomyopathy, since this is a condition driven by increased sympathetic drive and NE release. In this patient, NPY levels then decreased concomitant with functional recovery of the heart [152]. As a potent vasoconstrictor co-released with NE, NPY may induce transient coronary vasospasm in the stressed myocardium, contributing to the transient wall motion abnormalities that characterize this condition [153], however, this has yet to be proven.

Individuals with type II diabetes have also been reported to have higher serum levels of NPY [138, 154], whereas individuals with gestational diabetes do not [154]. Both Y_1 and Y_2 receptor levels were increased in human atrial biopsies from diabetic patients [138]. These authors also report a dramatic increase in Y_5 receptor labeling, predominantly in cardiomyocytes, in diabetic patient atrial biopsies [138]. Conversely, Ejaz et al. [48] reported no change in NPY protein levels, and reduced levels of Y_2 and Y_5 receptors in atrial biopsy samples from diabetic patients. The reasons for these discrepant findings are not clear; patients were of similar ages, had almost identical HbA1C levels, and were undergoing bypass surgery in both studies. There were an increased number of male patients in the diabetic group (92%) compared to the control group (74%) in the Matyal study [138], whereas the gender breakdown was not provided in the Ejaz study [48]. This could be one potential difference. Medication regimes and other underlying cardiac pathologies are other possibilities.

Despite these associations between NPY and heart failure, none of these studies establish a cause and effect relationship. Such studies are conflicting. Surprisingly, deletion of the Y_1 receptor in mice actually resulted in fibrosis in the heart [155]. However, isolated adult rat cardiomyocytes hypertrophied in response to NPY (10 and 100 nM) due to an increase in

protein synthesis and a down-regulation in protein degradation [156]. Hypertrophic effects of NPY on isolated adult SHR cardiomyocytes do not occur through the Y_1 receptor, but likely involve the Y_5 receptor [157]. In this instance NPY did not increase protein synthesis in non-hypertrophied cardiomyocytes from 8 week old SHR, but instead increased protein synthesis and mass in hypertrophic cardiomyocytes from 12–20 week old SHR [157]. Y_2 receptor antagonism had no effect on ventricular arrhythmias in a rat model of MI [158], however, Y_2 receptors mediate the pro-angiogenic actions of NPY [135]. NPY also induced cell death in isolated rat neonatal cardiomyocytes in a concentration-dependent manner (10–100 nM) [159], which correlated with decreased ATP. Transmission electron microscopy identified mitochondrial morphological abnormalities including collapsed cristae, as well as swollen and ruptured mitochondrial membranes. There was also a decline in mitochondrial membrane potential. These in vitro studies suggest that NPY could promote hypertrophy and cell death in cardiomyocytes, and the conclusion reached by McDermott and Bell [135] in their excellent review article on NPY and cardiac disease is that NPY may be more important in augmenting hypertrophy rather than initiating it.

While most data suggests a pathological role for NPY, Matyal et al., [160], using an interesting model of MI, found a protective role for this neuropeptide. Yorkshire miniswine were fed a high fat diet for five weeks before undergoing permanent occlusion of the left circumflex coronary artery for three weeks. After this, an osmotic minipump was placed so as to apply NPY_{3–36} (a cleaved product from NPY) directly to the infarct region for an additional four weeks. NPY was found to improve LV relaxation, perfusion to the ischemic area, angiogenesis, apoptosis, fibrosis, and oxidative stress (increased MnSOD). Unfortunately, it was not clear whether these parameters pertained to the infarcted region or the remote LV or both. Interestingly, administration of NPY in this model increased Y_1 and Y_5 receptors, but not Y_2 [161]. A potent vasoconstrictor, NPY would not typically be considered to provide the beneficial actions observed in this study. However, the effects seen occurred at a concentration of NPY much lower than that which causes vasoconstriction and systemic effects do not occur in this model [161]. Angiogenesis is probably a large component of the beneficial effects of NPY, although GLUT 4 was found to be significantly decreased on cardiomyocyte membranes and CPT1-M increased, suggesting that NPY may facilitate the use of fatty acid metabolism over the typical transition to glycolytic metabolism that occurs with ischemia. Whether this has benefits long term is unknown. Due to the conflicting nature of the reports on NPY it is difficult to know its function in cardiac disease and it may depend on etiology or time point in disease progression. NPY may have protective functions at low concentrations, but be pathological when higher amounts are present.

8.0 ANTI DIURETIC HORMONE (ADH, VASOPRESSIN, ARGININE VASOPRESSIN)

8.1 Localization and Physiological Actions in the Heart

ADH is a 9 amino acid peptide (Table 1) produced by the paraventricular and supraoptic hypothalamic nuclei in response to an increase in blood osmolarity, hypovolemia or hypotension. ADH is produced peripherally also, especially by cardiac tissue, specifically

cardiac microvascular endothelial cells [162]. This was evident from several studies showing the presence of ADH in aortas of rabbits and rats as well as in isolated perfused rat hearts with the levels increasing with an increase in pressure overload [163]. While ADH is rapidly cleared from plasma, the 39 amino acid C-terminal fragment of the proADH peptide, referred to as copeptin, is much more stable and hence provides a basis for measurement of ADH, especially in heart failure [164]. Three receptors have been identified for ADH, namely V₁ (also referred to as V_{1a}), V₂ and V₃, belonging to the rhodopsin-like G-protein receptor family [165]. V_{1a} receptors are located on both vascular smooth muscle cells as well as cardiomyocytes [166] (Table 1). The role of ADH in the vasculature is well established, while the cardiac effects are still unclear. In the vasculature, the physiological roles for ADH are related to maintaining blood osmolarity and blood pressure, in response to osmoreceptors and baroreceptors, respectively [167]. Mostly, the cardiac effects appear to be related to adverse remodeling as explained below.

8.2 ADH in Heart Failure

In relation to cardiac pathology, increased levels of ADH have been observed in both patients and rats with heart failure, by mechanisms involving an increase in preload [162]. During the developmental stages of heart failure, ADH release occurs in response to the reduced arterial pressure sensed by the baroreceptors [168]. In advanced heart failure, ADH is the major neurohormone maintaining fluid retention [162]. A study by Kelly et al. [164] demonstrated that copeptin levels predict LV remodeling and dysfunction in acute MI patients. An increased expression of the V_{1a} receptor has also been reported in heart failure [169].

In the heart itself, ADH increases the synthesis of protein, leading to cellular hypertrophy in cardiomyocytes [170]. ADH also promotes the proliferation of cardiac fibroblasts as well as upregulating the expression of endothelin-1 and connective tissue growth factor, leading to combined detrimental effects on ventricular remodeling [162]. However, one study [171], showed an increase in the total capillary density of the ventricle wall following administration of ADH in rats, which protects myocytes from transient ischemia. Another important mechanism through which ADH promotes heart failure is by the stimulation of aldosterone secretion, which in turn causes sodium and water retention, exacerbating diastolic wall stress in the failing heart [162]. The positive role for ADH antagonists, which cause the excretion of water while conserving sodium, have been reported as a possible treatment for congestive heart failure, replacing the use of hyponatremia-causing loop diuretics (see review by Rehsia and Dhalla for a summary of the outcomes of clinical trials based on this strategy) [168].

9.0 THYROID STIMULATING HORMONE (TSH)

9.1 TSH and Thyroid Hormones in Cardiovascular Physiology

TSH is a tropic glycoprotein hormone from the anterior pituitary gland, which controls the secretion of thyroid hormones T₃ and T₄ from the thyroid gland. It is made of 2 subunits – TSH α (92 amino acids) and TSH β (118 amino acids, Table 1). In an unusual fashion compared to other glycoprotein hormone receptors, the TSH receptor is formed after the

cleavage of a single polypeptide chain, and then the subsequent disulphide-linkage, into two subunits [172]. The thyroid hormones can subsequently influence the cardiovascular system in both physiological and pathological conditions.

Cardiomyocytes rely on serum T3, which binds to nuclear receptors $\alpha 1$ and $\beta 1$ (Table 1), and regulates genes of interest in cardiac function including the myosin heavy chain. For a list of all the cardiac-specific proteins regulated by T3, see review by Dan [173]. The non-genomic effects of T3 on the heart are broad, and are important in cardiac physiology. These include increased cardiac output (heart rate and contractility), an activation of sympathetic nervous system and the renin angiotensin system, and reduced vascular resistance [174]. Besides these, some of the other reported actions of T3 also include anti-apoptotic, anti-hypertrophic through multiple signaling pathways including MAPK kinases and ERK 1/2, anti-fibrotic by downregulating collagen I, anti-remodeling myocardial contractile effect through increases in SERCA-2, as well as anti-inflammatory through modulation of innate immunity [175].

9.2 TSH and Thyroid Hormones in Adverse Cardiac Remodeling

Cardiovascular complications in hyperthyroidism, including Grave's disease, are well reported. These include arrhythmias, pulmonary hypertension and increased cardiac output [176]. Factors affecting the increased cardiac output are related to both changes in heart rate and myocardial contractility, mediated through actions of hyperthyroidism on the sympathetic nervous system [176]. Experimental hyperthyroidism in rats causes LV hypertrophy in the absence of cardiac fibrosis. Interestingly though, these hyperthyroid hearts are stiffer due to increased calcium uptake through L-type calcium channels [177]. The general decrease in peripheral vascular resistance observed in hyperthyroidism can be related to excess production of nitric oxide [176]. Ultimately though, blood pressure increases in response to hyperthyroidism probably due to increased blood volume [178]. Interestingly, both hyperthyroidism and hypothyroidism have roles in atrial sympathetic remodeling that precedes atrial fibrillation [179]. The mechanisms involved are related to the upregulation of nerve growth factor (NGF), which influences the sprouting and survival of sympathetic neurons [179]. An increased hemodynamic load leading to increased cardiac hypertrophy is well established in hyperthyroidism [180]. In rat models of ventricular hypertrophy, re-expression of T3-inactivating enzyme D3 (a deiodinase mainly expressed only during embryonic development) was also reported [181]. In human heart failure, the abnormal thyroid function is mostly related to low T3 levels, which is also one of the powerful predictors of mortality in these patients, however, the levels of T4 and TSH are normal [182].

10.0 ADDITIONAL NEUROPEPTIDES

10.1 Catestatin

Catestatin is a 21 amino acid peptide that antagonizes nicotinic receptors [183]. It is one of multiple products that are the result of proteolytic cleavage of Chromogranin A, which is found mainly in chromaffin cells of the adrenal medulla and adrenergic neurons, but also cardiomyocytes [183]. In the cardiovascular system, catestatin has anti-hypertensive and

vasodilatory properties [183]. At a cardiac physiology level, isolated rat heart experiments have demonstrated that catestatin increases coronary perfusion pressure, but reduces LV pressure, rate pressure product (an index of cardiac work), and rates of contraction and relaxation [184]. Catestatin can act through the nicotinic receptor, however, this does not seem to be the mechanism of its cardiac effects [183].

A recent clinical study by Peng et al., [185] identified that elevated plasma levels of catestatin in chronic heart failure patients (n=202) correlated with all-cause death as well as cardiac-related death. Interestingly, those with increased plasma catestatin and BNP were at highest risk of all-cause and cardiac death. Xu et al., studied patients with acute ST-segment elevation myocardial infarction (STEMI, n=46), unstable angina pectoris (n=89), and no coronary artery disease (n=35) [186]. They found that plasma catestatin levels were lower in the STEMI and unstable angina groups compared to controls. Conversely, Meng et al., reported plasma catestatin to be elevated in STEMI patients at time of admission. These levels further increased during the first week post-MI, but had returned to control levels by three months post-MI. Catestatin correlated with anterior MI and LV ejection fraction in the acute stage. Similarly to the report of Peng et al., [185] patients with LV remodeling had higher levels of BNP and catestatin. The ability of exogenously administered catestatin to prevent adverse myocardial remodeling was examined using a rat model of acute MI, whereby catestatin (0.25 mg/kg/12 hrs, IP) was administered beginning 24 hours post-MI and continued for 28 days [187]. Consistent with its known function of opposing catecholamine release, catestatin reduced plasma epinephrine and NE levels post-MI. Catestatin also successfully reduced LV chamber size, improved systolic function, and provided some protection from ventricular arrhythmias. Beneficial effects of catestatin were further confirmed by ischemia reperfusion studies in isolated rat hearts [188]. Catestatin administered during the first 20 min of the 2 hr reperfusion period (following 30 min of ischemia), reduced apoptosis and infarct size in hearts from both WKY and SHR. This resulted in improved cardiac function. The protective effects of catestatin appear to involve HIF-1 α , eNOS, Akt, GSK3 β , and calcium channel S-nitrosylation [188, 189]. In addition to direct effects on cardiomyocytes, catestatin may also provide cardioprotection by indirect mechanisms since catestatin counteracts the actions of ET-1 on cardiac function [183]. Overall, catestatin levels increase in heart failure and evidence to date indicates a protective role for this neuropeptide. However, more studies are required to solidify this conclusion.

10.2 Secretogranin II/Secretoneurin

Secretoneurin is a 33 amino acid neuropeptide derived from secretogranin II stored in primary afferent (C-fiber) neurons, including in the heart [190]. Secretoneurin induces relaxation of porcine coronary arteries by an endothelium-dependent mechanism involving NO and COX pathways [191]. Secretogranin II levels are increased in the plasma of heart failure patients and like catestatin, correlate with BNP [192]. A more recent study found that plasma levels of secretoneurin in heart failure patients also correlated with N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T, but not with NE or ejection fraction [193]. Upon follow-up (median = 776 days, range = 246 to 983 days), secretoneurin levels were strongly correlated with mortality. Further, plasma secretoneurin was higher in patients with ventricular arrhythmias and those patients with more severe

damage have the highest levels of secretoneurin. In a mouse model of permanent myocardial ischemia and heart failure, both mRNA and protein levels of secretogranin II were increased in infarcted and remote regions of the heart, as well as in the circulation [192]. Secretogranin II was detected in cardiomyocytes, endothelial cells, fibroblasts, and cells infiltrating the infarct area. Infusion of secretoneurin, into isolated rat hearts undergoing 30 min of global ischemia and 2 hrs of reperfusion, reduced infarct area and LV end diastolic pressure [192]. Interestingly, treatment of isolated neonatal cardiomyocytes with NE and TGF- β 1 increased secretogranin II mRNA in these cells [192]. This did not occur with angiotensin II, ET-1, or TNF- α . Overexpression of secretoneurin by cardiac injection of secretoneurin-containing plasmid resulted in reduced LV volume, as well as and improved systolic and diastolic function four weeks after MI [194]. Interestingly, secretoneurin reduced the area of fibrosis (that included the scar region). Part of the cardioprotective effects of secretoneurin may include angiogenesis since increased numbers of capillaries were found in the peri-infarct region in secretoneurin-overexpressing hearts. In vitro experiments also showed that secretoneurin had a chemotactic effect on human coronary artery endothelial cells as well as promoting tube formation by these cells. Both actions involved VEGF and MAPK pathways. A receptor for secretoneurin has as yet not been identified, however, mouse cardiomyocytes have been shown to internalize secretoneurin [193]. Secretoneurin localized with endogenous Ca^{2+} /calmodulin-dependent protein kinase II delta (CaMKII δ) and calmodulin in intact perfused mouse hearts and reduced CaMKII δ autophosphorylation and activity. Furthermore, ryanodine receptor 2 (RyR2) phosphorylation was reduced by secretoneurin. RyR2 is the major channel responsible for the intracellular release of Ca^{2+} in cardiomyocytes, and its function is regulated by CaMKII δ phosphorylation. Phospholamban regulates Ca^{2+} re-uptake into the sarcoplasmic reticulum via modulation of sarcoplasmic reticulum Ca^{2+} transport ATPase 2 (SERCA2) and secretoneurin also reduced CaMKII δ -dependent phosphorylation of the Thr17 residue of phospholamban, but not PKA regulated Ser16 phosphorylation. Not surprisingly, secretoneurin reduced Ca^{2+} spark frequency within cardiomyocytes, as well as increasing Ca^{2+} transient amplitude and reducing transient decay [193]. Overall, Secretogranin II/Secretoneurin levels are increased in heart failure. There is evidence that this is a protective response, however, many more studies are needed to confirm this.

10.3 Galanin

Galanin is a 30 amino acid (29 aa in non-human species) peptide found in sympathetic neurons, and acts on the GalR1, GalR2, and GalR3 receptors, all of which are found in the heart [195, 196]. The cardiovascular effects of galanin are complex. In a guinea pig atrial preparation with dual autonomic innervation, galanin was shown to partially contribute to the reduced vagal bradycardia [195]. Interestingly, inhibition of the effects of NPY by Y_2 receptor blockade completely prevented the reduced vagal bradycardia. This demonstrates the cross-talk between sympathetic and vagal nerves that regulate cardiac function. In isolated guinea pig papillary muscle preparations, galanin exerted a bi-phasic effect on contractility with low concentrations being a positive inotrope and high concentrations having a negative inotropic effect [197]. At a pathological level, galanin mRNA levels in sympathetic neurons are increased one week post-ischemia reperfusion in rats, with myocardial galanin protein levels also increased [198]. That galanin was increased only in

the area of the LV distal to artery ligation was consistent with the concept that galanin may be transported to regenerating nerve endings. In myocytes, galanin improved contractile performance of papillary muscles following simulated ischemia reperfusion. However, induction of MI in rats treated with the GalR antagonist M40 (30 nmol/kg IP, for four weeks), showed that M40 imparted small improvements in ejection fraction and a slightly reduced LV chamber dimension compared with MI controls, resulting in a slightly reduced heart weight to body weight ratio [199]. This was accompanied by small reductions in BNP and IL-6, but not TNF- α . Similarly, fibrosis was reduced to a small degree, although it was not clear whether this was in the infarct/peri-infarct area or the remote region of the LV. The greatest effect of M40 was seen in the approximately 50% restoration of SERCA2 protein levels. However, the dynamics of galanin release may be etiology dependent with a recent study finding that plasma galanin was increased in obese patients (n=44) compared to lean controls (n=44), but that obese individuals with hypertension (n=38) had galanin levels equal to lean individuals [200]. Interestingly, in diabetic rats, galanin was important in regulating GLUT4 levels in the heart since the non-selective GalR antagonist M35 further decreased already reduced GLUT4 levels in diabetic rats [201]. This may indicate a role for galanin in trying to maintain GLUT4 levels and hence glucose uptake by cardiomyocytes in the diabetic heart. However, it is important to note that this was an STZ-induced model of diabetes. This action of galanin on cardiac GLUT4 is seemingly through the GalR1 since intracerebral infusion of the GalR1 agonist M617 induced a small, but significant increase in GLUT4 [202]. Interestingly, M617 also caused a small, but significant increase in GLUT4 in cardiac tissue in control rats. M617 also reduced fasting glucose levels in both control and diabetic animals in this study, thus, this could be the reason for altered cardiac GLUT4 levels as opposed to direct effects of galanin.

10.4 Neurokinin A (NKA)

Similarly to SP, NKA is a member of the tachykinin family of neuropeptides. NKA is a 10 amino acid peptide (Table 1) also encoded by the *Tac1* gene and is expressed in central and peripheral afferent sensory neurons [27, 28]. Since NKA is encoded from the β and γ isoforms of *Tac1*, its expression is always accompanied by the expression of SP. Hence both are often synthesized, stored and released together [27]. NKA induces its physiological effects mainly through the NK-2R (Table 1), although there is some overlap in between SP and NKA at the NK-1R and NK-2R [203].

Autoradiographic studies of the heart have revealed that NKA binding sites (NK-2R) are restricted to the intrinsic cardiac ganglia and coronary vessels with no detectable receptor in either atrial or ventricular myocardium [204]. This suggests that cardiac response to NKA occur primarily through stimulation of neural tissue. NKA has been shown to induce bradycardia, increase ventricular contraction and decrease perfusion pressure in guinea pig hearts and its effect is more potent than SP [205]. NKA has also been shown to induce coronary vasodilation although its potency in inducing such effect is significantly lower in comparison to SP [206, 207]. In addition, NKA is also able to induce constriction of coronary resistance vessels in guinea pigs [205, 207].

There is a major lack of studies dedicated to deciphering the role NKA in cardiac remodeling. NKA did tend to be increased in patients with congestive heart failure, but this did not reach statistical significance [101]. The NK-2R is expressed in inflammatory cells such as macrophages and dendritic cells [208–212], suggesting that it could play a role in the inflammatory response that often is a part of adverse cardiac remodeling. In a study by Kitamura et al., [212] they suggested that NK-2R mediated signaling is involved in host immune response such as cytokine release and antigen presentation by dendritic cells and the presence of an NK-2R antagonist, GR 159897 suppresses IFN- γ and IL-2 cytokine production. Thus, NKA could contribute indirectly to cardiac remodeling through the infiltration of immune cells and inflammation, but currently this is not established.

Although NKA has a strong affinity to bind to its receptor, the NK-2R, several lines of evidence suggested that NKA is also able to exert its effect through the NK-1R [213–217]. However, to date, this claim remains controversial as studies have shown contradictory results. An extensive study conducted by Tauer et al., [218] using NK-1R^{-/-} mice and selective high affinity non peptide NK-1R, NK-2R and NK-3R receptor antagonists revealed that there is a significant probability that the central actions of NKA could be mediated by a cross talk between NK-1R and NK-2R receptors. This study could be used as a reference point in studying the role of NKA in cardiac remodeling since isolated neonatal cardiomyocytes have been shown to express the gene for NK-1R and NK-3R receptors, though not NK-2R receptor.

11.0 SUMMARY AND FUTURE DIRECTIONS

The importance of neuropeptides to adverse cardiac remodeling and heart failure is under appreciated. General effects of each neuropeptide covered in this review are summarized in Figure 1. Of the neuropeptides discussed in this review, several such as CGRP, SP, SS, ADH, NPY and TSH/T3 have moderate to strong evidence supporting a causal role in this process (Table 2). CGRP is clearly cardioprotective, while SP is protective acutely following ischemia but promotes adverse remodeling chronically. SS counteracts cardiomegaly by reducing secretion of growth promoting hormones. ADH, NPY and TSH/T3 have effects on hemodynamics and cardiac hypertrophy. Catestatin and secretoneurin appear to be cardioprotective, although more work is needed to confirm this. For other neuropeptides including VIP, galanin, and NKA, their role in adverse cardiac remodeling and heart failure is less clear. The actions of these neuropeptides may differ depending on concentration with low amounts being protective and higher amounts having adverse effects. VIP may be an example of this. The temporal response may also be important for several of these neuropeptides. For example, SP has protective actions acutely following onset of pathology, but exerts adverse effects chronically. Regardless of the specific action of each neuropeptide, as a whole, these peptides represent important mediators of the underlying mechanisms that contribute to heart failure and as such deserve greater consideration as potential therapeutic targets.

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Figure 1.

Schematic depicting the actions of key neuropeptides in the setting of adverse cardiac remodeling and heart failure. SP = substance P, CGRP = calcitonin gene-related peptide, VIP = vasoactive intestinal peptide, SS = somatostatin, ADH = antidiuretic hormone, NPY = neuropeptide Y, TSH/T3 = thyroid stimulating hormone/ triiodothyronine, NT = Neurotensin.

Table 1

Neuropeptide receptors in the heart.

Neuropeptide	Amino Acids	Receptor(s) in the Heart
CGRP	37	CRL/RAMP1
SP	11	NK-1
SS	14	sst1, sst 2, sst 4, sst 5
VIP	28	VPAC1, VPAC2
NT	13	NTS ₁ , NTS ₂ , NTS ₃
NKA	10	NK-2
NPY	36	Y ₁ , Y ₂ , Y ₅
ADH	9	V ₁ (V _{1a})
TSH/T3	98(α)-118(β)	TSH (thyroid)/α1, β1
Catestatin	21	nAChR (antagonist)
Secretoneurin	33	Unknown
Galanin	30	GalR1, GalR2, GalR3

CGRP = calcitonin gene-related peptide, SP = substance P, SS = somatostatin, VIP = vasoactive intestinal peptide, NT = neurotensin, NPY = neuropeptide Y, ADH = antidiuretic hormone, TSH = thyroid stimulating hormone, T3 = triiodothyronine, nAChR = nicotinic acetylcholine receptor.

Table 2

Effect of neuropeptides in cardiac disease.

Cardioprotective	Promote Adverse Remodeling	Role Uncertain
CGRP	SP	NT
SP	NPY	NKA
SS (cardiomegaly)	ADH	
VIP	TSH/Thyroid hormones	
NPY	Galanin	
Catestatin		
Secretoneurin		

denotes strength of evidence.

= strong,

= moderate,

= weak.

CGRP = calcitonin gene-related peptide, SP = substance P, SS = somatostatin, VIP = vasoactive intestinal peptide, NT = neurotensin, NPY = neuropeptide Y, ADH = antidiuretic hormone, TSH = thyroid stimulating hormone