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Review

# Role of neuropeptides in cardiomyopathies

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ABSTRACT

The role of neuropeptides in cardiomyopathy-associated heart failure has been garnering more attention. Several neuropeptides – Neuropeptide Y (NPY), vasoactive intestinal peptide (VIP), calcitonin gene related peptide (CGRP), substance P (SP) and their receptors have been studied in the various types of cardiomyopathies. The data indicate associations with the strength of the association varying depending on the kind of neuropeptide and the nature of the cardiomyopathy – diabetic, ischemic, inflammatory, stress-induced or restrictive cardiomyopathy. Several neuropeptides appear to alter regulation of genes involved in heart failure. Demonstration of an association is an essential first step in proving causality or establishing a role for a factor in a disease. Understanding the complexity of neuropeptide function should be helpful in establishing new or optimal therapeutic strategies for the treatment of heart failure in cardiomyopathies.



**Contents**



## Introduction

Cardiomyopathies are myocardial disorders in which the heart muscle is structurally and/or functionally abnormal, and in which coronary artery disease, hypertension, valvular or congenital heart disease are absent or do not sufficiently explain the observed myocardial abnormality [17,34]. Cardiomyopathies can be divided according to whether they are primary – predominantly involve the heart, or secondary, where systemic disorders involve the heart [40]. Five categories of cardiomyopathies have been identified: dilated, hypertrophic, restrictive, arrhythmogenic right ventricular and unclassified cardiomyopathy [54]. Dilated cardiomyopathies include ischemic, inflammatory or diabetic cardiomyopathy. The etiology of cardiomyopathies encompass a large number of factors including genetic abnormalities, inflammation, accumulation of different substances within or between the cardiomyocytes, endocrine, neuromuscular, neurologic or nutritional disorders

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[38,39]. Because of the wide spectrum of types of cardiomyopathies, multiple etiologic factors have been identified or continue to be investigated.

There is growing interest in the role of neuropeptides to modulate the pathogenesis of some types of cardiomyopathies. Several neuropeptides have been identified and have been the subject of sufficient investigation to merit a review to examine the strength of the association with cardiomyopathy.

## Characteristic of neuropeptides

***Neuropeptide Y*** *(**NPY**)* is a 36-residue peptide amide produced by cleavage from a large precursor, preproNPY that is widely distributed in the central and peripheral nervous system. In the periphery, NPY is co-stored and co-released with noradrenaline in sympathetic nerve fibers. In the heart, NPY mRNA is expressed in the cell bodies of intrinsic neurons and endothelial cells. Its actions are mediated through G protein-coupled receptors denoted NPY1R-NPY6R. The actions of NPY in the heart are extensive and include practically every cardiac cell type. The Y1 receptor induces vasoconstriction and regulates protein turnover and constitutive gene expression in hypertrophying cardiomyocytes. Investigations to date have implicated the role of NPY in the pathology of a number of diseases including diabetes [52].

***Vasoactive intestinal peptide (VIP***) is a 28 amino acid peptide that belongs to a family of structurally related peptide hormones that includes also ***pituitary adenylate cyclase-activating peptide (PACAP)***. They are widely distributed in the nervous system, where they act as neurotransmitters. Their biological effects are mediated by specific receptors, VPAC1 and VPAC2, which have comparable affinity for VIP and PACAP, and PAC1 that binds VIP with 1,000-fold lower affinity than PACAP. Both peptides are involved in autonomic regulation of the cardiovascular system, where they exert positive inotropic and chronotropic effects, and cause coronary vasodilatation. Additionally, PACAP inhibits proliferation of cardiac fibroblasts [12].

***Calcitonin gene related peptide (CGRP), adrenomedullin (AM)*** *and* ***intermedin (IMD)*** are structurally related peptides belonging to the same peptide family [22]. CGRP**,** a 37 amino acid peptide, is the major neuropeptide released from sensory nerve terminals in the heart [18], where increases heart rate and contractile force, and due to its potent vasodilatory effect increase coronary artery perfusion [46,69]. Additionally, it induces hypertrophy of cardiomyocytes [25]. CGRP exerts cardioprotective functions of ischemic preconditioning [34]. AM is a 52 amino acid peptide, which is widely distributed in a variety of cell types including cardiomyocytes and endothelial cells [5,65]. In the heart, AM is released in response to hypoxia [5], and the AM signaling system is upregulated during ischemic heart failure in rats [50]. IMD, also known as adrenomedullin 2, is a novel peptide, recently discovered simultaneously by 2 groups [56,68]. IMD may exert cardioprotection in experimental heart disease models including congestive heart failure and ischemia/reperfusion injury [21,79]. The biological actions of this family are attributed to their actions at three receptor subtypes comprising the calcitonin receptor-like receptor (CRLR) complexed with one of three receptor activity modifying proteins (RAMP1-3).

***Substance P (SP)*** is an 11 amino acid peptide amide that has been associated with many physiological processes in the cardiovascular system. In the periphery, SP is co-stored with CGRP in a special class of nociceptive neurons that has both afferent and efferent functions. SP/CGRP-containing sensory nerve fibers within the heart derive from cell bodies located in the dorsal root ganglia and nodose ganglia. Peripheral processes of these neurons innervate intrinsic cardiac ganglia and coronary arteries. SP has also been classified as a mammalian neurokinin (NK) or endokinin which acts through G protein-coupled receptors denoted NK1-NK3 [51]. The actions of SP in the heart are extensive and include indirect negative chronotropic and inotropic effects by stimulating cholinergic neurons [9]. Additionally, SP exerts direct and indirect stimulatory effect on cardiomyocytes and cardiac fibroblasts [9].

## Role and mechanism of neuropeptides in cardiomyopathy

### *Stress cardiomyopathy*

Stress cardiomyopathy is an atypical form of cardiac pathology primarily induced by stressors, mostly psychological or physical. Some authors referred this as Tako-Tsubo cardiomyopathy. The etiology of stress-induced cardiomyopathy has not been fully elucidated, probably several mechanisms are involved including multivessel coronary artery spasm, coronary microvasculature dysfunction, acute coronary syndrome with spontaneous reperfusion, transient left ventricular outflow obstruction and catecholamine mediated myocardial dysfunction [1,49]. NPY was the only neuropeptide which involvement has been studied in etiology of stress cardiomyopathy.

In the rat model, **NPY** may play an important role in the pathogenesis of stress cardiomyopathy. Immunohistochemistry showed a higher production of NPY in the hearts of male rats, subjected to immobilization stress and low voltage electric foot shock, compared to those in the control group [2]. In the stress-subjects, there was an overflow of NPY in cardiac tissue [2]. This finding is supported by the observation of increased NPY serum level in patients with stress cardiomyopathy [66]. NPY is potent vasoconstrictor. Its release can induce intense coronary vessels spasm and repeated episodes of coronary spasm can lead to focal cardiomyocyte injury which is consistent with the histopathologic changes associated with stress cardiomyopathy [71].

### *Diabetic cardiomyopathy*

Diabetic cardiomyopathy refers to a condition which affects the myocardium in some persons with diabetes mellitus. Diabetic cardiomyopathy appears to be a frequently unrecognized pathological process in asymptomatic diabetic patients [44]. A frequently used animal model of human diabetic cardiomyopathy is a rat model of type I diabetes, which is induced by single application of streptozotocin (STZ) [8]. Extensive metabolic perturbations lead to the morphological and functional changes of the diabetic myocardium. These alterations include abnormalities of cardiac neural innervation. Nerve fibers that innervate the heart are damaged, leading to both parasympathetic and sympathetic dysfunction [61,62]. Intracardiac ganglia show morphological derangements with swollen mitochondria, accumulation of neurofilaments and neurotubules [28]. Neuropeptides released by these nerve fibers may further impair cardiac function. Cardiac autonomic neuropathy plays an important role in the development of left ventricular dysfunction and is associated with increased cardiovascular risk in diabetic patients [78]. Clinical manifestation of diabetic cardiac neuropathy, painless myocardial ischemia and reduced heart rate variability, are found in patients with long-term diabetes mellitus [19,23].

**NPY** plasma levels are increased in diabetes mellitus in human and animal studies [24,41,60]. In the heart, the level of NPY was lower in the patients with type II diabetes mellitus [16,41], as well as in the hearts of patients with end-stage heart failure due to idiopathic dilated cardiomyopathy, which at the time of cardiac transplantation show significantly lower levels of NPY [3]. Receptors for NPY have been studied in the diabetic heart. Gene and protein expression of NPY1R were not different between