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Review

Substance P in heart failure: The good and the bad ☆

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ABSTRACT

The tachykinin, substance P, is found primarily in sensory nerves. In the heart, substance P-containing nerve fibers are often found surrounding coronary vessels, making them ideally situated to sense changes in the myocardial environment. Recent studies in rodents have identified substance P as having dual roles in the heart, depending on disease etiology and/or timing. Thus far, these studies indicate that substance P may be protective acutely following ischemia-reperfusion, but damaging long-term in non-ischemic induced remodeling and heart failure. Sensory nerves may be at the apex of the cascade of events leading to heart failure, therefore, they make a promising potential therapeutic target that warrants increased investigation.

1. Introduction

Substance P is from the tachykinin family of sensory nerve neuropeptides. The other classic members of this family are neurokinin A (NKA) and neurokinin B (NKB). While NKB is encoded for by its own gene (*TAC2*) and is restricted to the central nervous system, substance P and NKA are both encoded by the *TAC1* gene and are found in the central nervous system and peripheral afferent sensory neurons [1,2]. The *TAC1* gene expresses pre-mRNA that can generate four mRNA isoforms (α, β, γ, and δ). All four isoforms give rise to substance P, whereas only the β and γ isoforms encode for NKA. This means that substance P can be expressed without NKA, however, NKA will always be accompanied by substance P. However, since the β and γ isoforms appear to be the most common, substance P and NKA will often be synthesized, stored, and released together [1]. Substance P acts primarily through the neurokinin (NK)-1 receptor, while NKA exerts its effects *via* the NK-2 receptor, although there is some overlap between the two [3]. The actions of tachykinins are many, but include smooth muscle contraction, vasodilation, nociception, and modulation of inflammatory/immune cell function [4–8]. Substance P and NKA have long been known to have negative inotropic and chronotropic effects on the normal heart [9,10], but it is only recently that we are beginning to consider that sensory nerve neuropeptides may have key roles in regulating adverse myocardial remodeling and the subsequent development of heart failure. Outside of the aforementioned effects on heart rate and contraction, little has been published relating to NKA and myocardial remodeling. Accordingly, this article will focus on substance P. What makes substance P so interesting is that recent experimental studies have revealed two sides to this neuropeptide in myocardial remodeling and heart failure; the good and the bad. Accordingly, the purpose of this review is to draw attention to the role of substance P in adverse myocardial remodeling and heart failure, since to this point in time it's role in these events have not been studied in detail. As such, this review will: 1) describe the localization of substance P within the myocardium; 2) describe the beneficial role of substance P acutely following ischemia reperfusion; 3) describe the detrimental role of substance P in long-term remodeling of the heart; 4) describe the direct effects of substance P on cardiomyocytes, cardiac fibroblasts, and cardiac inflammatory cells; and 5) discuss the clinical implications of substance P in the heart.

2. Substance P localization in the heart

Before discussing the good and the bad of substance P, it is necessary to understand the localization of this peptide in the heart (Table 1). This is what makes it ideally placed to rapidly respond to changes in the myocardial environment.

2.1. Substance P-containing nerves in the heart

Substance P is considered a neuropeptide, being produced primarily by C-fiber sensory nerves. Descriptions of the distribution of substance P-containing nerves in the heart are extensive, at least in rodents. The most extensive studies have been performed in guinea pig hearts.

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Table 1
Localization of substance P in the heart by species.

Species	Substance P localization	References
Guinea pig	Blood vessels, atria, ventricle (endocardium, epicardium, musculature), valves, papillary muscle, bundle of His, intrinsic cardiac ganglia	[11–15]
Rat	Atria, left ventricle (epicardium, musculature), blood vessels	[14,16]
Mouse	Intrinsic cardiac ganglia, intrinsic nerve bundles	[17]
Feline	Atria, ventricle (endocardium)	[20]
Canine	Left anterior descending coronary artery, circumflex artery	[21]
Non-human primate	Atria, intrinsic cardiac ganglia, blood vessels, musculature	[22]
Human	Intrinsic cardiac ganglia, blood vessels, musculature	[23–27]

Musculature refers to nerve fibers running between cardiomyocytes and does not mean substance P within cardiomyocytes.

2.1.1. Guinea pig

Many studies have identified substance P-containing nerves in the guinea pig heart. The following studies are not exhaustive, but are meant to be representative of the overall findings. Reinecke et al. [11] were the first to describe substance P-containing nerve fibers in the hearts of mammals in 1980. They reported that the entire coronary arterial system of the guinea pig heart was innervated by substance P-containing nerves. Hougland and Hoover [12] subsequently found that abundant numbers of substance P-containing nerve fibers were also present in the endo-, epi-, and myocardial regions of the atria and ventricles, as well as the mitral and tricuspid valves. Nerve fibers in the myocardial regions tended to run in parallel with cardiomyocytes. Meanwhile, Wharton et al. [13] described identifying more endocardial than epicardial substance P-containing nerves, particularly around the trabeculae and papillary muscles of the ventricles. There are no apparent differences between the left and right ventricles, however, more fibers are located at the base of the heart than at the apex [12,13]. In the ventricular septum, substance P-containing nerve fibers were associated with branches of the bundle of His [13]. Substance P-containing fibers are also associated with the ascending aorta and pulmonary trunk [12]. Papka and Urban [14] also observed substance P-containing neurons in the epicardium and musculature of the atria, the atrioventricular valves, and pericellular baskets around intrinsic cardiac ganglia. They also identified numerous substance P-containing nerve fibers in the parietal portion of the pericardium. Consistent with these findings, Dalsgaard et al. [15] also found many substance P-containing fibers in the atria, with fewer in the ventricles and mainly associated with blood vessels. Radioimmunoassay analysis of frozen heart samples revealed that substance P levels were roughly four times higher in the right atria compared to the left ventricle [15]. Interestingly though, in the left ventricle the levels of substance P were almost identical to the levels of epinephrine (4.2 ± 0.6 and 4.0 ± 0.4 pmol/g, respectively).

2.1.2. Rat

In contrast to the guinea pig, Hougland and Hoover [12] were unable to detect any substance P-containing nerve fibers in the rat heart. Subsequently though, Papka and Urban [14] were able to identify substance P-containing fibers in both the atrial and ventricular epicardium and myocardium of the rat heart. However, these were relatively few compared to the guinea pig heart. Radioimmunoassay analysis has confirmed this difference, with Holzer et al. [16] reporting 0.33 pmol/g of substance P in the rat heart, while Wharton et al. [13] and Dalsgaard et al. [15] reported 2.7 and 4.2 pmol/g respectively in the guinea pig left ventricle.

2.1.3. Mouse

To the authors knowledge there is only one published article describing substance P localization in the mouse heart. This is somewhat surprising considering the wide spread use of mice for studying cardiac disease. Rysevaite et al. [17], evaluated substance P-containing nerves in the intrinsic cardiac neural plexus. They found substance P-containing nerves to be most abundant in the epicardium and in ganglia adjacent to the heart hilum (the portion of the heart bounded by the serous pericardium above the heart base, ascending aorta and pulmonary trunk). These nerves were mainly thin, mixed with choline acetyltransferase and tyrosine hydroxylase-containing nerve fibers, and located close to blood vessels. In addition to being identified within the ganglia, substance P-containing nerves were also found in the intrinsic nerve bundles and interganglionic nerves. Since this study was focused on the intrinsic cardiac ganglia, they did not explore substance P-containing nerves within the ventricles of the mouse heart. D'Souza et al. [18] reported 2807 pg of substance P/mg of protein in mice with myocarditis, compared to 71 pg/mg in uninfected mice. This shows the extent to which substance P can be increased in the heart in a disease state. Similar substance P levels were also reported by Robinson et al. [19], also in mice with myocarditis. Since it was necessary to concentrate the samples for these assays, those values cannot be directly compared to those described for guinea pig and rat hearts.

2.1.4. Felines/canines

Fewer studies have investigated the spatial location of substance P-containing nerves in the cat and dog heart, and in far less detail. Zhu and Dey [20] described substance P-containing nerves in the atrial and ventricular myocardium as well as the endocardium in cats. In dogs, radioimmunoassay detection found that the left anterior descending coronary artery and circumflex coronary artery contain substance P [21].

2.1.5. Non-human primates

In the interatrial septum, both varicose and non-varicose nerve fibers have been identified as being substance P positive in the cardiac ganglia and musculature of the monkey heart (Macaca fascicularis) [22]. Substance P-containing nerves were found to form perivascular networks around blood vessels and to traverse muscle fibers.

2.1.6. Humans

In the human heart itself, Wharton et al. [23] reported relatively few substance P-containing neurons, with some occurring mainly around neural cell bodies in intrinsic ganglia and in nerve trunks. Hoover et al. [24] reported that substance P was observed in nerve fibers from the right atrial ganglionated plexus from patients undergoing coronary artery bypass grafting. In endomyocardial biopsies from patients with congestive or hypertrophic cardiomyopathies, Weihe et al. [25] found that all patients had substance P-containing nerve fibers close to arterioles, capillaries and veins. Substance P-containing nerve fibers have also been found surrounding the adventitia of coronary vessels in atherosclerotic regions of human coronary arteries [26]. In atrial biopsies taken from patients undergoing open-heart surgery (disease etiology not described), substance P-containing nerves were identified between cardiomyocytes and around blood vessels [27].

2.2. Origins of substance P-containing myocardial nerves

Bilateral removal of the stellate ganglia resulted in a marked reduction in substance P in the right atria of the guinea pig heart [15]. Vagus nerve depletion with capsaicin also decreased substance P in the right atria. Conversely, neither intervention affected substance P in the left ventricle, suggesting separate origins of ventricular substance P-containing nerves that lie outside the stellate ganglia [15]. Occlusion of the left anterior descending coronary artery in rats, resulted in an increase in substance P in the T4 region of the spinal cord [28] as determined by microprobes coated in substance P antibody. Similarly, spontaneously hypertensive rats (SHR) were found by immunofluorescence to have more substance P in their dorsal root ganglia than the normotensive Wistar Kyoto rat (WKY) [29]. In fact, sensory nerves from the dog ventricle have been traced to dorsal root ganglia in the T_3 region of