Chromogranin A: friend or foe of the failing myocardium?

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This editorial refers to ‘Myocardial production of chromogranin A in human heart: a new regulatory peptide of cardiac function’ by M. Pieroni et al., on page 1117

Chronic heart failure is defined as the inability of the heart to meet the circulatory demands of the organism. While cardiac injury, e.g. of ischaemic, toxic, metabolic, or genetic cause, is the initial abnormality, secondary changes occur over the course of the disease affecting most organ systems. This leads to a variety of pathologic changes including endothelial, pulmonary, hepatic, renal, endocrine and skeletal muscle abnormalities, and the state of multi-organ impairment in chronic heart failure is now considered the syndrome of chronic heart failure.

A neuroendocrine activation has been described early in the stages of heart failure research with the demonstration of elevated levels of norepinephrine and epinephrine in patients with dilated and ischaemic cardiomyopathy. While initially thought to be a compensatory and protective mechanism, it has been shown that it in fact leads to increased myocardial oxygen demand, structural damage, myocardial apoptosis, and results in the suppression of myocardial β-adrenergic receptors which through a negative feed-back mechanisms leads to further increase in circulating levels of norepinephrine and epinephrine. Blockade of β-adrenergic receptors, initially highly controversial, has been shown to be one of the most effective pharmacologic interventions in patients with chronic heart failure converting an at first hand counterintuitive intervention into a life-saving treatment, which is now part of the standard regimen of patients with chronic heart failure.

Among the increasing number of mediators of the neuroendocrine activation in chronic heart failure are the renin-angiotensin-aldosterone system and proinflammatory cytokines (such as tumor necrosis factor-alpha, TNF-α, and interleukin 1-beta, IL-1β). While inhibition of the renin-angiotensin-aldosterone system in chronic heart failure has been clearly demonstrated to be comparably effective as the blockade of the β-adrenergic system, interventions targeting proinflammatory cytokines or their receptors have so far not been shown to be effective in patients with chronic heart failure. In fact, detrimental effects were observed after blockade of the TNF-α system in patients with chronic heart failure.

Pieroni et al. describe the local expression of chromogranin A in human myocardium and its myocardial regulation in patients with chronic heart failure. Chromogranin A is a 49 kDa protein stored in secretory granules of several endocrine and neuronal cells and can be released by exocytosis. Proteolytic modification seems tissue-specific and results in various biologically active peptides. Vasostatins, the amino-terminal proteolytic fragments of chromogranin A, are released by sympathetic nerve terminals and inhibit arterial vasoconstriction. Further, vasostatins exert a negative inotropic effect on isolated hearts and counteract the actions of adrenergic drugs.

The authors analysed samples from patients with dilated cardiomyopathy and hypertrophic cardiomyopathy and found elevated myocardial expression levels of chromogranin A in both diseases as compared to controls. Expression levels of chromogranin A correlated with brain natriuretic peptide (BNP). Further, the authors describe increased circulating levels of chromogranin A in patients with dilated cardiomyopathy and hypertrophic cardiomyopathy compared to controls. The authors conclude their study with the demonstration of negative inotropic effects of recombinant vasostatin, a cleavage product of full-length chromogranin A, on isolated and perfused rat hearts.

The myocardial expression of chromogranin A may serve not only as a response to injury but might also participate in the molecular pathways during myocardial remodelling in chronic heart failure. The authors here demonstrate negative inotropic effects of vasostatin A, a cleavage product of full-length chromogranin A. The addition of vasostatin blocks β-adrenergic effects in the heart. This intriguing finding parallels the inhibition of an enhanced β-adrenergic activation in chronic heart failure by β-receptor blocking molecules. Therefore, one might hypothesize that the expression of chromogranin A is an endogenous autocrine/paracrine response mechanism in damaged myocardium with protective effects counteracting the enhanced β-adrenergic activation in chronic heart failure. Notably, chromogranin A is activated not only in dilated and hypertrophic cardiomyopathy but also in ischaemic myocardium. On the other hand, chromogranin A has been shown to affect fibroblast activation and endothelial activation and cell adhesion. This molecule and its cleavage products, therefore, might also contribute in cardiac remodelling with negative effects.
Elevated myocardial expression levels are accompanied by increased circulating levels of chromogranin A in patients with chronic heart failure. While the heart seems to function as a source of this molecule, others potential sources need to be identified. It is in fact unlikely that the entire circulating pool of chromogranin A originates from damaged myocardium. Interestingly, the exact origin of other molecules with increased myocardial and circulating levels in chronic heart failure such as TNF-α or IL-1β is still not completely identified. Nevertheless, the remodelling heart acts as an endocrine organ.

The processing of chromogranin A leads to cleavage at the amino-terminus of the protein and results in the production of vasostatin-1. While the current study does not differentiate between chromogranin A and vasostatin-1 in regard to their specific myocardial expression levels, vasostatin-1 seems to be responsible for the functional effects on the myocardium. It is unclear how chromogranin A is processed in the myocardium. However, the proteolytic modification appears crucial for the biologic effects of chromogranin A/vasostatin-1.

Altogether, the authors add a fascinating new piece to the expanding puzzle of neuroendocrine activation in patients with chronic heart failure. Clearly, this system will attract further attention and many open questions remain to be answered. We might speculate that the identification and functional characterization of molecules and proteolytic enzymes involved in this myocardial response system will lead to the description of new targets for therapeutic interventions in the syndrome of chronic heart failure.

Conflict of Interest: none declared.

References