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Review

The interplay between chromogranin A-derived peptides and cardiac natriuretic peptides in cardioprotection against catecholamine-evoked stress

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ABSTRACT

Chromogranin A (CgA) is the major soluble protein co-stored and co-released with catecholamines (CAs) from secretory vesicles in the adrenal medulla chromaffin cells. Present in the diffuse neuroendocrine system, it has also been detected in rat and human cardiac secretory granules where it co-stores with natriuretic peptide hormones (NPs).

Mounting evidence shows that CgA is a marker of cardiovascular dysfunctions (essential hypertension, hypertrophic and dilatative cardiomyopathy, heart failure) and precursor of the cardioactive peptides vasostatin-1 (VS-1) and catestatin (Cts). This review focuses on recent knowledge regarding the myocardial, coronary and anti-adrenergic actions of VS-1. In particular, the negative inotropism, lusitropism and coronary dilation effects of rat CgA1–64 (rCgA) and human recombinant STACgA1–78 (hrSTACgA1–78) are summarized with attention on their counteracting isoproterenol- and endothelin-1-induced positive inotropism, as well as ET-1-dependent coronary constriction. The interactions between vasostatins (VSs), NPs and CA receptors are proposed as a paradigm of the heart capacity to organize complex connection–integration processes for maintaining homeostasis under intense cardio-excitatory stimuli (myocardial stress).

Contents

Abbreviations: CgA, chromogranin A; CAs, catecholamines; NPs, natriuretic Peptides; VS-1, vasostatin 1; Cts, catestatin; rCgA1–64, rat CgA1–64; hrSTACgA1–78, human recombinant STACgA1–78; VSs, vasostatins; ET-1, endothelin 1; HPA, hypothalamus-pituitary-adrenal axis; NE, Noradrenaline; E, adrenaline; RAS, renin–angiotensin system; ANP, atrial natriuretic peptides; BNP, B-type natriuretic peptide; LVEDP, left ventricle end diastolic pressure; bCgA1–431, bovin CgA1–431; hCgA1–439, human CgA1–439; rCgA1–448, rat CgA1–448; hrVS-1, human recombinant VS-1; VS-2, vasostatin 2; rCgA1–64S-S, rCgA1–64 with intact S–S bridge; rCgA1–64SH, rCgA1–64 without S–S bridge; rCgA1–64OX, rCgA1–64 oxidized; HR, heart rate; LVP, left ventricular pressure; RPP, rate pressure product; −(LVdP/dt)max, maximal rate of left ventricular pressure decline; +(LVdP/dt)max, maximal rate of left ventricular pressure contraction; ISO, isoproterenol; BAE-1, bovine aortic endothelial cells; NO, nitric oxide; PKG, protein kinase G; PKA, protein kinase A; eNOS, endothelial nitric oxide synthase; PLB, phospholamban; SR, sarcoplasmic reticulum; pGC, particulate guanylate cyclase; sGC, soluble guanylate cyclase; PDEs, phosphodiesterases; PDE1, phosphodiesterases 1; PDE2, phosphodiesterases 2; PDE3, phosphodiesterases 3; PDE4, phosphodiesterases 4; PDE5, phosphodiesterases 5; CNP, C-type natriuretic peptide; VNP, ventricular natriuretic peptide.

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1. Introduction

The pioneering work of Claude Bernard (1867) on the brain–heart connection recognized the major regulatory role exerted on the heart by the autonomic nervous system, the adrenergic sympatho-excitatory (SNS) and the cholinergic inhibitory vagal (PNS) circuits, establishing the foundation of the neurovisceral control. This concept was further elaborated at the beginning of the 20th century by Walter Cannon in his view of the sympatho-excitatory vigilance or preparation for action, i.e. the "fight or flight response". These important studies paved the way to bridge the gap between cognitive processes, neuroscience and visceral physiology [1]. A few years after Cannon's studies, Selye [2] in his "stress response" (or "general adaptation syndrome") theory developed the concept of visceral organ dysfunction. Subsequently, he showed the prevalent role of the peripheral limbs of the stress system, the SNS and the hypothalamus-pituitary-adrenal (HPA) axis, in maintaining the stress-related homeostasis through the synergistic action of increased levels of CAs and glucocorticoids [3]. As a case study of a stressed-injured organ, Selye described the electrolyte-steroid cardiomyopathy, in which the heart is convergently targeted by the autonomic nerve terminal-released CAs (mainly noradrenaline, NE) and the circulating adrenaline (E) secreted by the adrenal medulla. An extensive body of research revealed the cardiovascular system as a typical paradigm of a stress-threatened organ, particularly under condition of allostatic load (prolonged threaten homeostasis), i.e. a state of excess wear and tear on the system [4]. The adrenergic overstimulation (augmented discharge of the SNS and increased circulating CAs) together with the activation of other excitatory loops (e.g. renin–angiotensin system) was recognized as a neuroendocrine hallmark of the stressed heart and vasculature. The PNS inhibitory circuits were viewed as the major counterbalancing effectors of these excitatory pathways. However, following the 1981 discovery [5] of the cardiac natriuretic peptides that established the concept of the heart as an endocrine organ [6], other important mechanisms of cardiac self-counter-regulation have been delineated. These include a number of regulatory peptides and autacoids produced and released by either the autonomic neurons supplying the heart and blood vessels, and/or various cell (myocardial, endothelial, smooth muscle, fibroblasts, and chromaffin) populations of the heart. This knowledge formed the mindset behind the biomedically-oriented search for natural principles to be used as diagnostic and therapeutic tools in cardiovascular function under normal and pathological conditions, including stress, myocardial hypertrophy and heart failure.

In this article we seek to provide an overview of the recent knowledge supporting a cardiac role for the anti-adrenergic CgA-derived VSs, particularly VS-1. We will summarize the VSs-induced cardiac actions on basal and chemically (adrenergic)-stimulated hearts together with a brief account on their action mechanisms. Lastly, we will consider the importance of the interactions between VSs, NPs and receptors for CAs as a paradigm of the heart capacity to maintain homeostasis. Some pertinent connection–integration processes activated under intense cardio-excitatory stimuli, such as the CA-induced myocardial stress, will be illustrated.

2. The "specific" secretory granules of the heart

The concept of the heart as an endocrine organ able to produce a growing number of hormonal modulators traces an interesting history.

Kish [7] and Bompiani et al. [8] revealed the presence of particular inclusions within the atrial cardiomyocytes of guinea pig and rat, which later were ultrastructurally characterized as "specific" by Palade [9] and Jamieson and Palade [10]. Since their number decreased after reserpine treatment, Jamieson and Palade [10] suggested that the granules were a storage site for CAs, exerting also a putative endocrine function to be further/later specified. However, fractional purification of specific atrial granules did not support the view that these granules are a site of storage of noradrenaline [11,12]. The endocrine hypothesis was supported by several investigations that emphasized the protein nature of the granule content. In the following years the extensive evidence documenting the presence of these granules in vertebrates, particularly in cyclostomes, fish and amphibians [reviewed by 13–15], provided a convincing comparative perspective of their old evolutionary roots. The discovery of the "atrial natriuretic factor" (ANF) as a major constituent of rat atrial granules with potent diuretic and natriuretic effects [5,6], firmly established the non-neuronal cells' ability of the vertebrate heart to synthesize and release peptide hormones *sensu strictu*. Ubiquitous in both mammalian and non-mammalian vertebrates [14,16–20], NPs were shown to link blood volume expansion and myocardial stretch through a homeostatic loop able to regulate cardiovascular performance *via* concerted multi-target effects on heart, vasculature, kidney, adrenal glands, as well as central and autonomic nervous system [21,22]. In the last decade this counter-regulatory network was enriched by the demonstration of the cardio-suppressive and anti-adrenergic actions elicited by the CgA-derived peptides VS-1 and Cts [23–27]. The recognition that the major myoendocrine granule constituent CgA, through the production of cardio-inhibitory principles, counteracts the most relevant CA-induced hemodynamic effects, is an important development [15,28]. In an updated context regarding the heart, this anti-adrenergic action of CgA-derived peptides allows to hypothesize that, as in the chromaffin cells of the adrenal medulla, where CgA and CAs are co-stored and co-released in the secretory granule [29,30], also in the heart a parallel release of CAs and CgA could contribute to cardiac counter-regulatory processes.

3. Cardiac co-localization of CgA and NPs: from biology to physiopathology

It has been documented that in the rat heart CgA is stored in non-adrenergic myoendocrine atrial cells containing atrial natriuretic peptide [31], in Purkinje fibres of the atrium and ventricle containing the calcium channel alpha 1E subunit [32], and in the sympathetic nerve termini [33]. In particular, immunohistochemical evidence showed in rat myoendocrine granules the co-localization of CgA and ANP, where the former, according to immunoblotting, appears processed more extensively than in the adrenal medulla [31]. The contribution of CgA-derived fragments released from intracardiac nerve terminals remains to be assessed [33]. As mentioned, apart from an intracellular role in secretory vesicle biogenesis [34], CgA exerts an important extracellular function as a prohormone for a number of shorter biologically active peptides produced by tissue-specific proteolytic processing [35 for references]. Importantly, the intracardiac processing of CgA documented in the rat heart showed the presence of four endogenous N-terminal CgA-derived peptides (CgA4–113, CgA1–124, CgA1–135 and CgA1–199) containing the VSs sequence [36]. Among these CgA fragments, the presence of intact CgA and various long C-terminal truncated CgA fragments was indicated by a major immunoreactive band of 80–50 kDa, corresponding to the apparent molecular mass of intact rat CgA (with and without post-translational modifications) [36]. Since CgA processing into small fragments is cell-specific [see, for example, 37,38], these data suggest an incomplete and specific maturation process in the heart. Importantly, among the other low-molecular-mass fragments identified, the cardioactive motif, i.e. the VS-1 sequence or a portion of it, is present. Therefore, the possibility exists that in response to a specific stimulus-induced proteolytic activation, elicited either under normal or stressful conditions, an increased lower molecular-mass fragment may be generated, with consequent autocrine/paracrine regulation of cardiac function.

Immunohistochemical evidence of CgA-positive intracellular staining showed that in ventricular myocytes of dilated and