Editorial

Nucleoside diphosphate kinase: a new player in heart failure?

Ying-Ying Zhou, Michael Artman*

Pediatric Cardiology, TWR Suite 9-V, NYU Medical Center, 540 First Avenue, New York, NY 10016, USA

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See article by Lutz et al. [33] (pages 48–55) in this issue.

Despite considerable efforts, the incidence, prevalence and mortality of heart failure remain high in most industrialized countries [1,2]. This is partially due to the complex nature of the heart failure syndrome. As a final outcome of many types of heart disease, the degree of heart failure varies from case to case depending on the pathological history, genetic basis and environmental background. However, the most common feature of the failing heart is diminished systolic and/or diastolic function, associated with disturbed intracellular Ca\(^{2+}\) homeostasis. Under physiological conditions, cardiac contraction is initiated by Ca\(^{2+}\) influx through sarcolemmal L-type Ca\(^{2+}\) channels, which subsequently triggers a large amount of Ca\(^{2+}\) release from the internal sarcoplasmic reticulum (SR) stores via ryanodine receptors. The increased intracellular Ca\(^{2+}\) activates the contractile myofilaments, and then is either recycled back into the SR by SR Ca\(^{2+}\) pumps or extruded out of the cell via sarcolemmal Na\(^{+}\) –Ca\(^{2+}\) exchanger, resulting in cardiac muscle relaxation. Profound alterations in Ca\(^{2+}\) handling proteins such as phospholamban, SR Ca\(^{2+}\) pump, Na\(^{+}\) –Ca\(^{2+}\) exchanger, contractile myofilaments and coupling between L-type Ca\(^{2+}\) channel and ryanodine receptor have been shown in failing hearts [3–5]. Restoration of these Ca\(^{2+}\) handling deficits is expected to have beneficial effects in patients with heart failure.

The intracellular second messenger, cyclic adenosine monophosphate (cAMP), activates cAMP-dependent protein kinase A, which subsequently phosphorylates many of the cardiac excitation–contraction components (including L-type Ca\(^{2+}\) channel, ryanodine receptor, Na\(^{+}\) –Ca\(^{2+}\) exchanger, myofilament proteins and phospholamban).

Phosphorylation of these Ca\(^{2+}\) handling proteins leads to positive chronotropic, inotropic and lusitropic effects, which provide support for the failing heart. β-Adrenergic stimulation, as the most potent natural cAMP generator and the primary regulatory mechanism of cardiac function in the normal heart, was among the first choice of treatments for heart failure patients [6]. Another reason for β-adrenergic receptors as the target for heart failure treatments is that diminished cardiac response to β-adrenergic stimulation (associated with a selective down regulation of β\(_{1}\)-adrenergic receptors, upregulation of β-ARK1 and an increase in G\(_{i}\) proteins) is well documented in heart failure. However, several clinical trials revealed that even though the hemodynamic symptoms were improved shortly after administration of β-adrenergic receptor agonists, chronic administration increased mortality in treated patients [7,8]. Similarly, other attempts aimed at improving contractile function by raising intracellular cAMP level using cyclic nucleotide phosphodiesterase (PDE) inhibitors results in increased mortality during chronic administration in heart failure patients [9–11]. Furthermore, transgenic mice overexpressing β\(_{1}\)-adrenergic receptors [12] or G\(_{i}\)a [13] also demonstrate an initial positive inotropic effect followed by subsequent cardiac hypertrophy and heart failure.

Taken together, the above results seem to suggest that activation of β-adrenergic receptor/cAMP system may provide a short-term hemodynamic improvement, but damages the failing heart in the long run. Thus, the reduced cardiac contractile response to β-adrenergic receptor stimulation (attributed to selective downregulation of β\(_{1}\)-adrenergic receptors, upregulation of β-ARK1 and an increase in G\(_{i}\) proteins) might be considered to be a beneficial compensatory effect to the high plasma catecholamine levels observed in patients with heart failure [14]. From this perspective, β-adrenergic receptor antagonists instead of agonists should be favorable for the chronic treatment of heart failure. Indeed, accumulating evidence indicates that β-adrenergic receptor blockers improve ventricular function and increase survival in heart failure.

*Corresponding author. Tel.: +1-212-263-5993; fax: +1-212-263-5808.
E-mail address: michael.artman@med.nyu.edu (M. Artman).
patients [15–17]. Interestingly, \(\beta\)-adrenergic receptor blockade also arrests myocyte damage and prevents the development of heart failure in the transgenic \(G_{\alpha_{i}}\) mouse [18].

We are now learning that the situation is probably more complicated than we originally thought. For example, while \(\beta_{1}\)-adrenergic receptor subtype overexpression induces cardiomyopathy [12], cardiac-specific overexpression of \(\beta_{2}\)-adrenergic receptor subtype markedly enhances cardiac function without evident cellular or cardiac hypertrophy [19]. Moreover, overexpression of \(\beta_{2}\)-adrenergic receptor at low levels [20] or overexpression of adenylyl cyclase [21] to increase cAMP, rescues cardiac function and/or reverses cardiac hypertrophy in \(G_{\alpha_{i}}\) overexpression mouse model. In addition, overexpression of \(\beta\)-ARK1 inhibitor increases both basal and isoproterenol-mediated contractility and prevents the development of dilated cardiomyopathy phenotype in muscle-specific LIM domain protein (MLP) knockout heart [22].

How can we reconcile these apparently disparate lines of evidence? One emerging possibility is that the same second messenger, cAMP, may produce different functional consequence depending on how cAMP is generated. It has been well known that cAMP from different sources might exist in different intracellular compartments. For example, both \(\beta_{1}\)- and \(\beta_{2}\)-adrenergic receptor stimulation increase total cellular cAMP levels to a similar extent in rat cardiac myocytes, but the augmentation of cAMP in the particulate fraction is higher for \(\beta_{1}\)-adrenergic receptor stimulation than that for \(\beta_{2}\)-adrenergic receptor stimulation [23]. While activation of \(\beta_{1}\)-adrenergic receptor phosphorylates both sarcolemmal (Ca\(^{2+}\) channel) and cytoplasmic proteins (phospholamban, glycogen phosphorylase kinase, troponin I and C), activation of \(\beta_{2}\)-adrenergic receptor only modulates sarcolemmal Ca\(^{2+}\) channel without phosphorylation of non-sarcolemmal proteins [24]. Functionally, \(\beta_{1}\)-adrenergic stimulation in rat cardiac myocytes elicits not only positive inotropic effects, but also enhanced lusitropy and spontaneous Ca\(^{2+}\) oscillations. In contrast, the latter effects are absent during \(\beta_{2}\)-adrenergic stimulation [25]. More surprisingly, \(\beta_{1}\)- and \(\beta_{2}\)-adrenergic receptor subtypes exert opposite effects in the apoptosis process: \(\beta_{1}\)-adrenergic stimulation strongly induces apoptosis whereas \(\beta_{2}\)-adrenergic stimulation protects cardiac myocytes from apoptosis [26]. Therefore, spatially distinct cAMP signals generated by different \(\beta\)-adrenergic receptor subtypes provide a mechanism by which a single second messenger can produce diverse final outcomes. Emerging evidence also suggests that spatially localized cAMP signaling can be achieved by various active receptor states [27,28], different anchoring proteins [29,30] and various isoforms of protein kinases [30] or phosphatases [31]. For the treatment of heart failure, it might be important to choose the cAMP-generating mechanisms that selectively enhance beneficial effects such as contractile support, but avoid adverse effects such as apoptosis or Ca\(^{2+}\) oscillations (for review see Ref. [32]).

In this issue of Cardiovascular Research, Niroomand and colleagues [33] identified a new signal transduction mechanism, NM23-nucleoside diphosphate kinase (NDPK), which might be involved in the alteration of cAMP signaling during heart failure. NDPK, a conserved enzyme throughout evolution, catalyzes non-substrate-specific conversion of nucleoside diphosphates to nucleoside triphosphates and participates in a wide range of biological functions including gene regulation, cell growth, development, metabolism and signal transduction. NDPK has been found in hearts from many species [34]. The membrane associated NDPK can activate G proteins by catalyzing the transfer of a phosphate from ATP to GDP (forming ADP and GTP). This pathway provides a novel mechanism to modulate cAMP level independent of receptor-G protein interaction. However, the net effect of NDPK depends on the relative prevalence of \(G_{i}\) and \(G_{q}\) since all G proteins are presumably activated non-selectively by NDPK. In canine cardiac sarcolemmal membranes, activation of NDPK stimulates adenylyl cyclase and increases cAMP levels [35], whereas in normal human cardiac sarcolemmal membrane, inhibition of NDPK has no effect on adenylyl cyclase activity [33]. The important finding by Niroomand and his colleagues [33] is that both the protein level and the activity of NDPK are significantly increased in human failing hearts as compared to non-failing controls. Interestingly, these changes are limited to the sarcolemmal membrane and are not observed in the cytosol or other membrane fractions. While basal adenylyl cyclase activities are similar between the two groups, stimulation of adenylyl cyclase activity by physiological concentrations of GDP and ATP is greater in control hearts than in failing hearts. The authors contend that this difference is mainly due to the greater inhibitory effect of NDPK on adenylyl cyclase activity in failing hearts. These results provide the first evidence that sarcolemmal membrane-associated NDPK is up regulated during heart failure and may serve as a novel mechanism contributing to the diminished cAMP signaling observed in the failing heart.

This work [33] may have important implications in the heart failure field because alterations in cAMP signaling are not only one of the intrinsic mechanisms for the development of cardiac dysfunction, but in addition represent key molecular targets for the treatment of failing heart. As discussed above, the lack of efficient prevention and treatment of heart failure is partially due to the complicated roles of cAMP from different sources or compartments. The discovery of NDPK as a new member in cAMP signaling cascade might provide another piece of information to help solve this puzzle. Meanwhile, this intriguing result also raises many interesting aspects for future studies: What is the mechanism(s) for the alteration of sarcolemmal membrane-associated NDPK in heart
failure? Is it a cause or a result of heart failure? Is it adaptive or deleterious to the prognosis of heart failure? Since the effect of NDPK is relatively non-selective, it can modulate diverse targets inside cardiac myocytes including potassium channels [34,36]. Thus, effects beyond alteration of contractile function should also be considered when exploring the role of NDPK in the failing heart. Finally, investigation of receptor-dependent and receptor-independent cAMP pathways with regard to the subcellular distribution and function of cAMP may shed new light on existing concepts of signaling mechanisms. Finding answers to the questions above will help us to better understand the mechanisms of heart failure and ultimately, to develop novel and more rational approaches to prevent and treat heart failure.

References


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