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Clinical pharmacology of cardiac cyclic AMP in human heart failure: too much or too little?

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Abstract

Introduction: Cyclic 3`, 5`-adenosine monophosphate (cAMP) is a major signaling hub in cardiac physiology. Although cAMP signaling has been extensively studied in cardiac cells and animal models of heart failure (HF), not much is known about its actual amount present inside human failing or non-failing cardiomyocytes. Since many drugs used in HF work via cAMP, it is crucial to determine the status of its intracellular levels in failing vs. normal human hearts.

Areas covered: Only studies performed in explanted/excised cardiac tissues from patients were examined. Studies that contained no data from human hearts or no data on cAMP levels per se were excluded from this perspectivès analysis.

Expert opinion: Currently, there is no consensus on the status of cAMP levels in human failing vs. non-failing hearts. Several studies in animal models may suggest maladaptive (e.g., pro-apoptotic) effects for cAMP in HF, advocating for cAMP lowering for therapy, but human studies almost universally indicate that myocardial cAMP levels are deficient in human failing hearts. It is the expert opinion of this perspective that intracellular cAMP levels are too low in human failing hearts, contributing to the disease. Strategies to increase (restore), not decrease, these levels should be pursued in human HF.

Keywords

Adenylyl cyclase; Cardiac function; Cyclic AMP; G protein-coupled receptor; Heart failure; Human heart; Phosphodiesterase; Protein kinase A; Signal transduction

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Declaration of interest

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1. Introduction

Since its seminal discovery in the late 1950`s by Earl Sutherland and colleagues, prompting him to coin the term “second messenger” for such molecules that form inside the cell in response to an extracellular signal (“first messenger”), cyclic 3`, 5`-adenosine monophosphate (cAMP) has been found to play central roles in almost every signaling pathway inside every cell type [1]. This Nobel prize-awarded discovery laid the foundation for the signal transduction field. cAMP is synthesized from adenosine triphosphate (ATP) at the cell membrane by specific enzymes, the adenylyl cyclases (ACs), which, however, lack extracellular segments and do not bind extracellular molecules [2]. In the following decades, additional Nobel prize-awarded work by Alfred Gilman and Martin Rodbell but also by Bob Lefkowitz, Brian Kobilka, and others, elucidated how ACs get activated by extracellular stimuli, i.e., that the stimulus binds to, and activates a specific plasma membrane-residing heptahelical receptor, which, in turn, activates one of several guanine nucleotide-binding (G) proteins residing nearby at the cell membrane. One of these G proteins, Gs, binds and activates AC after its interaction with the receptor (a G protein–coupled receptor, GPCR) [3–8]. G proteins are heterotrimers of a, b, and g subunits, with the a subunit either stimulating AC activity (Gas) or inhibiting it (Gai), resulting in increased or decreased intracellular cAMP levels, respectively [2,3]. Certain Gbg subunits (a dimer that functions as a monomer) can also modulate AC activity [2]. 10 mammalian AC isoforms exist, nine cell membrane-bound (AC1–9) and one soluble (cytosolic AC10, responding to bicarbonate instead of the cell membrane-embedded GPCR) [2]. cAMP signals are transduced by several effector proteins with which it directly interacts, including protein kinase A (PKA or cAMP-dependent protein kinase), the exchange protein directly activated by cAMP (Epac), cyclic nucleotide–gated (CNG) ion channels, and the Popeye domain-containing (POPDC) proteins [9–13]. At least eleven different types of phosphodiesterase (PDE1–11) exist in mammalian cells, responsible for termination of cAMP action. Three of them (PDE5, −6, −9) degrade exclusively cyclic 3`, 5`-guanosine monophosphate (cGMP), while the other eight terminate the life of cAMP in cells (PDE4, −7, −8 are cAMP-specific; PDE1, −2, −3, −10, −11 have dual cAMP/cGMP specificity) [14–16]. Importantly, PDEs are encoded by multiple genes with multiple splice variants or alternative promoters, so the number of PDE isoforms in mammals is quite vast (over 100 functional PDE isoforms have been identified to date) [14–16]. Finally, cAMP and cGMP crosstalk to each other directly via PDE activity regulation, e.g., cGMP modulates certain cAMP terminating PDE activity and vice versa [14–16].

2. Beneficial actions of myocardial cAMP

The central role of cAMP in virtually every signaling mechanism leading to contractile augmentation (positive inotropy) inside the cardiomyocyte is very well known and documented [17–20] (Figure 1). Specifically, cAMP elevates intracellular [Ca^{2+}] via PKA-mediated phosphorylation of plasma membrane voltage-gated L-type calcium channels (LTCCs) and sarcoplasmic reticulum (SR) membrane ryanodine receptor (RyR2) channels, which directly stimulates stronger interactions of myosin fibers with actin filaments thereby increasing inotropy [17–20] (Figure 1). Recent evidence suggests that PKA-dependent activation of LTCCs may involve not only direct phosphorylation of the channel but also inhibitory phosphorylation of the LTCC inhibitor protein Rad [21–23]. Of note, LTCCs and

RyR2 are only the chief targets of cAMP promoting contractility via this extremely versatile Ser/Thr kinase (PKA), estimated to have over 200 different protein substrates on average inside every cell [24]. Numerous additional effects via this or its other effectors contribute to the positive inotropy afforded by cAMP, some of which (esp. via Epac1/2 or POPDC proteins) still await elucidation.

The role of cAMP in automaticity (pacemaker activity) and positive dromotropy (myocardial conductivity) is also quite well documented. cAMP operates Hyperpolarization-activated Cyclic Nucleotide-gated (HCN)-4 (and HCN-2) channels, responsible for the generation of the pacemaker "funny" current (If) in sinoatrial (SA) nodal pacemaker cells [12] (Figure 1). It also augments depolarizing Ca^{2+} influx currents (via LTCCs) in atrioventricular (AV) nodal cells, responsible for propagation of electrical conduction throughout the atria, AV node, and over to the ventricles (Purkinje fibers and Hiss bundle) [19] (Figure 1).

An equally central role is played by cAMP in cardiac relaxation (positive lusitropy). The importance of this sometimes gets diluted by the focus given on cAMP`s actions towards positive inotropy. Nevertheless, cAMP is essential for cardiac relaxation, a process necessary for proper ventricular filling during diastole, which, in turn, is a critical determinant of cardiac function, i.e., of the force of the next contraction (based on the Frank-Starling law of normal cardiac operation) [25,26] (Figure 1). Additionally, proper diastolic function is important for cardiac muscle oxygenation and nourishment, as the coronary arteries can only deliver blood to the cardiac cells during diastole (compressed during systole/contraction) [25,26]. PKA is again the main mediator of cAMP`s effects in cardiac relaxation. PKA lowers free intracellular [Ca^{2+}] (removes Ca^{2+} from the cytosol) via SERCA2a activation in the SR membrane (by phosphorylating phospholamban) and Na^+/K^+-ATPase (NKA) activation in the plasma membrane (by phosphorylating phospholemman), which induces the Na^+/Ca^{2+}-exchanger (NCX) to remove Ca^{2+} out of the cardiomyocyte [17,19] (Figure 1). At the same time, PKA reduces Ca^{2+} sensitivity of actomyosin filaments and increases their distensibility via phosphorylation of cardiac troponin I (cTnI), titin, and cardiac myosin-binding protein-C3 (MyBPC3) [27–29] (Figure 1).

3. Is cAMP up or down in the failing HUMAN heart?

There is a lot of confusion regarding the actual status of cAMP synthesis/levels in human HF or even if it matters at all [30], mainly emanating from the myriad basic science studies with experimental animal models of HF that oftentimes report contradicting or conflicting results, depending on the type of experimental HF, animal species, use of whole heart tissue or isolated cardiac cell types (or cell lines), and other experimental parameters/ details of each study [31]. This perspective is focused solely on the situation in human failing hearts in vivo and attempts to shed light on what really happens to steady state cardiac cAMP levels in HF patients, regardless of the status of activity or compartmentation of its various effectors (mainly PKA, anchored to nanodomains by A kinase-anchoring proteins (AKAPs). Besides, it is quite plausible that cAMP signaling nanodomains might be organized/assembled already at the plasma membrane by the AC itself, i.e., the very source of the synthesized cAMP [32].

In the failing human heart with systolic dysfunction, i.e., HF with reduced ejection fraction (HFrEF) of any etiology, gene expression (mRNA and/or protein levels) of certain AC isoforms may or may not be altered but the overall (total) plasma membrane AC activity and synthesized cAMP levels, both basal and hormone-stimulated, seem to be lower (Figure 1) [33,34]. This is mainly because a certain isoform of Gαi (the AC-inhibitory G protein subunits), but not Gαs, is significantly upregulated in both acute and chronic end-stage human HF and in both ischemic and dilated human cardiomyopathies [35–40] (Figure 1). This probably reflects an adaptive response of the failing human myocardium to shield itself from the toxic effects of the chronic norepinephrine (sympathetic) overstimulation of its adrenergic receptors (ARs) and is, in fact, mediated by cAMP itself (b_1AR-induced cAMP upregulates Gαi transcriptionally via the cAMP-response element binding (CREB) transcription factor) [40]. Importantly, in one of the first studies on cAMP signaling in human failing hearts, before the discovery of the Gai upregulation, both basal and isoproterenol-stimulated cAMP synthesis were found to be deficient [41]. The inotropic response to forskolin, a labdane diterpene (4 isoprene units) that directly activates AC, was preserved in failing human heart tissue, indicating no change in AC expression levels, but the response to PDE inhibitors, including caffeine and the inotrope drug milrinone, was reduced, unless a minimally effective dose of forskolin to boost cAMP levels was administered first [41]. These striking results strongly suggested that, not only the bAR (isoproterenol)-stimulated, but also the basal cAMP synthesis were markedly repressed in the failing human heart, which bodes well with the subsequent reports of Gαi elevation in human HF. Additionally, this seminal study demonstrated that the inotropic response of the failing human heart to extracellular [Ca^{2+}] (Ca^{2+} "loading") was also preserved [41], i.e., pro-contractile Ca^{2+}-handling proteins that promote increased free intracellular [Ca^{2+}] do not appear altered in the failing human heart, although the ones that promote relaxation (SERCA2a) might be [35]. Further evidence for decreased total AC catalytic activity and hence, reduced cAMP synthesis, in human failing hearts has been provided by a few other studies, which showed that no matter what changes the mRNA or protein expression of individual AC isoforms undergo in human HF and via which mechanism, total AC activity is generally lower in advanced stage failing human hearts of various disease etiologies [33,42,43]. This well-established finding was, in fact, the impetus for AC6 gene therapy entering clinical trials for human HF treatment a few years ago [44,45].

In addition to its repressed synthesis, cAMP degradation may also be elevated in the failing human heart, since, out of the cAMP-degrading PDEs expressed in the heart (PDE1, −2, −3, −4, and −8), at least cardiac PDE1 and PDE2 activities are elevated in various types of human HF [14,46,47]. Of course, the exact picture of individual cAMP-terminating PDE activities in failing human hearts is quite complicated and the net effect on total cAMP hydrolysis is ill-defined [48–52]. For instance, PDE3A, in contrast with PDE1 and PDE2, has been reported to be downregulated in failing human hearts [48]. However, this partial PDE3 downregulation observed in human left ventricles from dilated and ischemic cardiomyopathy patients seems to affect mainly cGMP, rather than cAMP, levels [49], while PDE4, also potentially downregulated in human failing hearts, seems to affect cAMP levels only in specific subcellular compartments rather than the global (total) cardiac cAMP levels [52]. Besides, the combined contribution of PDE3 and PDE4 in cAMP hydrolysis

in human ventricular myocytes has been assessed and found to be considerably less (albeit still significant) than that of PDE1 [53]. Taken together, the net status of cAMP degradation in human failing hearts is still under investigation. However, cAMP synthesis is clearly suppressed and thus, steady state, global intracellular cAMP levels are almost certainly lower in the failing vs. the non-failing human myocardium.

4. Are the suppressed cardiac cAMP levels good or bad for the HF patient?

A common misconception is that high cAMP levels are bad for the heart, because cAMP mediates the positive inotropy of catecholamines, increasing cardiac workload, oxygen and metabolic demands, arrhythmogenesis, etc., and because it is believed to mediate the pro-apoptotic b_1AR signaling in the failing myocardium [31,54]. Therefore, the apparent deficiency in cAMP production must be an adaptive mechanism of the failing myocardium to protect itself against the excess sympathetic nervous system activity. Although it is true that cAMP increases positive inotropy and the metabolic demand of the myocardium, it is also absolutely essential, as mentioned above, for cardiac diastolic function. It is also essential for counterbalancing the excessive cholinergic-dependent hyperpolarizing currents (hyperpolarizing K^+ current activated by acetylcholine, IKACh) in the atria predisposing to bradycardia/arrhythmias, including atrial fibrillation [55]. Additionally, cAMP exerts various additional effects that can be to the benefit of the not only functionally but also structurally compromised failing myocardium (due to adverse remodeling). Indeed, myocardial cAMP antagonizes hypertrophy (PKA phosphorylates and inhibits nuclear factor of activated T cells (NFATc)-dependent pro-hypertrophic and pro-inflammatory gene expression [14,56]), inhibits apoptosis and fibrosis via both PKA and Epac [14,57–59], as well as inflammation (e.g., PKA inhibits NFATc and the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome [56,60]) and oxidative stress (PKA phosphorylates and blocks NADPH oxidase (NOX)-2 [61]). All these effects aid reverse remodeling of the failing heart rather than adverse remodeling, which is always promoted by Ca^{2+} signaling and $G_{q/11}$ protein-coupled receptors that induce it [14,17,62,63]. On the other hand, despite the low cardiac cAMP levels, norepinephrine levels remain high, cardiac function continues to decline, and adverse remodeling goes on throughout the course of human HF, unless treated with medications, including the once unheard of, but now part of cornerstone HF pharmacotherapy, b-blockers [64]. If cAMP lowering were an advantageous, adaptive mechanism for the failing heart, then why are the b-blockers still needed to improve quality of life of the HF patient? By the way, b-blockers may indirectly increase or at least preserve basal cardiac cAMP levels (i.e., not reduce them), as suggested by some studies in patients [65] and in recombinant cells in vitro [66], but also by in vivo studies of these agents on feedback upregulation of bARs [67] and on downregulation of GPCR-kinase (GRK)-2 (see below) [68]. It is thus more likely that cAMP deficiency mainfests itself as an adaptive/compensatory initial response of the myocardium to the acutely elevated norepinephrine levels (sympathetic nervous system activation) but quickly turns into a maladaptive process, further compromising the function and homeostasis of the failing human myocardium.

5. More evidence from the cardiac bAR changes in human HF

General dysfunction of almost the entire cardiac bAR signaling apparatus is a well-established hallmark of human HF [64,69]. b_1AR levels, normally ~75% of the total bAR complement of adult human hearts [67], are down (selectively downregulated), the remaining b_1ARs and the b_2ARs (now residing at roughly equal numbers in the cell membrane of the failing cardiomyocyte) are desensitized, i.e., uncoupled from Gs proteins, thanks to elevated GRK2 and barrestin1 activities [69], and, as mentioned above, Gai-mediated inhibition of AC is markedly increased, while Gαs levels are unaltered (or slightly down). Furthermore, since the function of b_1- and b_2ARs is strongly suppressed, the excess norepinephrine released locally in the failing heart is now diverted to the b_3AR [70]. This subtype, like the b_1- but unlike the b_2AR, has higher affinity for norepinephrine than epinephrine and, despite being minimally expressed (less than 5% of total bARs in normal human myocardium) is the only bAR subtype that still functions normally in HF due to its inability to get desensitized by GRKs/arrestins [70]. Unfortunately for the failing human heart however, cardiac b_3AR couples to $G_{i/o}$ protein/nitric oxide-dependent negative inotropy, instead of AC/cAMP-dependent positive inotropy [71,72]. Thus, cAMP synthesis still cannot be stimulated, and the failing human heart continues to pay the price, i.e., malfunction. Taken together, these alterations in the failing human myocardium`s bAR apparatus signal a profound deficiency/depletion of its cAMP “supply”.

6. Expert opinion

The vast majority (if not the totality) of studies done in explanted human cardiac tissue over the past 40 years clearly point to a marked reduction in the capacity of the failing human heart to sustain the cAMP levels necessary to perform its housekeeping functions. The falloffs in cardiac function and cAMP levels strikingly parallel each other in human HF. cAMP exerts beneficial (not toxic) actions in the failing heart, and its augmentation/restoration, not further suppression, should be pursued therapeutically for human HF. In fact, the AC activator forskolin has been used for centuries in Indian traditional medicine as a medical herb (plant root extract) for various conditions including heart disease and HF [73]. The inherent inability of the failing human heart to increase its cAMP content due to bAR dysfunction or Gai and PDE upregulation may explain, at least in part, why bAR agonists (“sympathomimetics”) and other positive inotropes like the PDE3 inhibitor milrinone have failed in clinical trials for chronic HF therapy. Although this notion has recently been challenged by long term studies and meta-analyses [74], milrinone is considered to increase mortality due to cAMP increase; hence, cardiac cAMP increase should be avoided for HFrEF (systolic HF) therapy. On the other hand, the findings that basal AC activity is down and PDE3 inhibitors do not seem able to increase cardiac cAMP substantially [49,53], seem to diametrically contradict this notion. In fact, the exact opposite might be the case: milrinone may not be able to improve HF mortality in the long run exactly because it cannot increase cardiac cAMP. Alternatively, milrinonès effect on mortality might be a property specific to this agent, since other PDE3 inhibitors (e.g., olprinone) exert cardioprotective effects in the post-myocardial infarction (MI) heart via increasing cAMP [57]. This could also very well be the reason for the apparent failure of glucagon-like peptide (GLP)-1 receptor agonists, such as semaglutide and liraglutide, in clinical trials for HFrEF, although

they appear to have significant therapeutic potential in HF with preserved ejection fraction (HFpEF) [75]. This drug class also works through cAMP (the GLP-1 and glucagon receptors are Gs-coupled), which is why glucagon and GLP-1 agonists exert positive inotropy and are occasionally used in acute decompensated HF (e.g., if the patient is on b-blockers). Finally, milrinone blocks PDE3, which also terminates cGMP [14], and, given that chronic cGMP-dependent protein kinase (PKG) activation can exacerbate stress-induced cardiomyopathy [76], milrinonès (debatable) lack of mortality benefit may be due to some unique effects mediated by chronically increased cGMP.

In conclusion, the notion that cardiac cAMP increase is damaging for the failing heart is a misconception. In human failing hearts, chronic cAMP levels are severely reduced, causing or precipitating all kinds of dysfunction and structural adverse remodeling. It should be emphasized here that this conclusion is inferred by data in non-manipulated, excised human cardiac tissue only, which is the closest someone can get to a snapshot of the real situation inside the failing human myocardium in vivo. Studies in animal models or in vitro studies in cultured cells (including altered human cardiomyocytes) have not been taken into account in this perspective, given they were done in artificially altered settings (transgenic animals with interspecies differences, transfected cells, cells from explanted hearts changing physiology as they transition into in vitro culture).

Therefore, cAMP-elevating agents like AC activators or PDE inhibitors, especially if combined with sympatholysis to lower norepinephrine levels, such as that afforded by b-blockers, have enormous therapeutic potential in human HFrEF of all stages and of virtually all etiologies. Another attractive class of agents that can elevate cAMP levels indirectly are positive modulators of Regulator of G protein Signaling (RGS) proteins, specifically those that deactivate Gi/o proteins (R7 family members of RGS proteins) without affecting Gs proteins [19,77,78]. Given the enormous challenges of developing AC type-specific activators and the highly cell type- and receptor-type specific action of these RGS proteins, positive modulators of Gai-deactivating RGS proteins [79,80] might be the most attractive and realistic pharmacological approach for cAMP elevation in the failing human heart, outside of the gene therapy approach with AC6 gene delivery already in clinical trials [44,45]. Obviously, the therapeutic cAMP elevation must be carefully finetuned, so it results in restoration of the depleted cAMP levels in failing human hearts and does not exceed those of non-failing hearts. This point warrants caution because excess cAMP can potentially lead to the opposite extremes, i.e., adverse effects like arrhythmias, ischemia, apoptosis, etc. [81–83], although the actual severity of these risks, especially in humans, is presently unknown and could be minimal based on studies reporting direct cardioprotective effects of cAMP in failing hearts [56–58].

Of note, cAMP`s beneficial effects in other tissues outside the myocardium (which, however, indirectly affect cardiac function and morphology, such as adipose tissue and endocrine glands regulating intermediary metabolism) are well documented. Specifically, cAMP seems to exert beneficial effects in obesity and aging (as mentioned above, GLP1 agonists like semaglutide, FDA-approved for weight loss, work through cAMP elevation) [84–86], but also in dermatologic and autoimmune inflammation [87,88], and, based on very recent preclinical and clinical evidence, even in alcohol use disorder (apremilast, as an inhibitor of

the cAMP-specific PDE4, inhibits inflammation and accelerates hangover recovery through cAMP elevation) [89], In fact, PDE4 inhibition that exclusively leads to increased cAMP levels is increasingly used for new off-label indications in dermatology [90]. Therefore, it will be hardly surprising if, someday, cAMP stimulation has become a pharmacological "holy grail" for a long and healthy life.

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Article highlights

- cAMP is crucial not only for the systolic but also for the diastolic function of the heart, either one of which (or sometimes both) are impaired in human HF.
- Studies in cultured cells in vitro and in animal models in vivo either do not report actual intracellular cAMP levels in failing hearts or give a complicated and confusing picture.
- Albeit very few and far between, essentially all the studies reported in the literature that directly measured cAMP levels in human hearts found cAMP production deficient in the failing human myocardium regardless of etiology.
- Studies measuring levels or examining the functional status of cAMP-associated proteins in human failing hearts, such as the three b-adrenergic receptor subtypes, G protein expression, adenylyl cyclase activity, and certain types of cAMP-degrading phosphodiesterases, tend to corroborate the findings of deficient cAMP levels in failing human hearts, compared to normal ones.
- Based on the above, the present article concludes that one of the major culprits for the dysfunction of the failing human heart is its deficit of cAMP, instead of cAMP itself.
- Strategies to increase/restore total steady state cytoplasmic cAMP levels inside human failing cardiomyocytes, either with RGS protein modulators or AC gene therapy, should be beneficial for the failing human heart and must be pursued for human HF therapy, alongside existing approaches, such as phosphodiesterase inhibition.

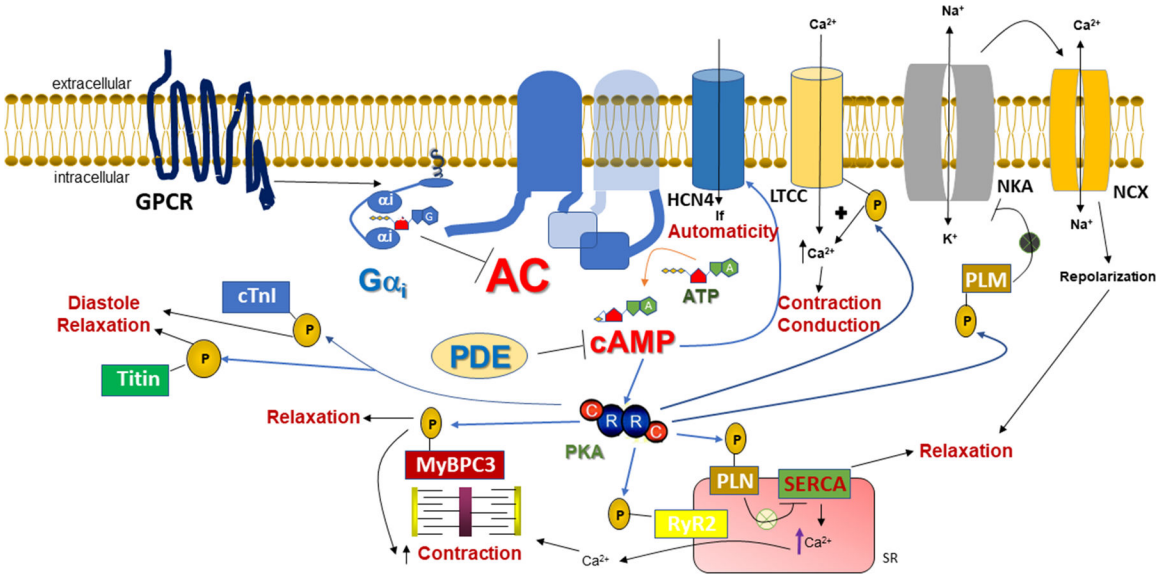

Figure 1. Roles of cAMP in cardiac function.

Schematic illustration of the main effects of cAMP (via PKA) in cardiac inotropy, lusitropy, chronotropy, automaticity, and dromotropy. Not all pathways and effects are shown (e.g., Epac-mediated effects are omitted) for more clarity. Molecules or enzymes that are decreased in the failing human heart are shown in red fonts (AC activity, cAMP), while those that are increased in light blue fonts (Gai, PDE activity). Phosphorylation of MyBPC3 by PKA enhances both contraction and relaxation.

A: Adenine; AC: Adenylyl cyclase; ATP: Adenosine triphosphate; cAMP: Cyclic 3`,5`-adenosine monophosphate; C: Catalytic subunit of PKA; cTnI: Cardiac troponin I; G: Guanine; Gai: Inhibitory G protein alpha subunit; HCN4: Hyperpolarization-activated Cyclic Nucleotide-gated (HCN)-4 cation channel; If: “Funny” (pacemaker) current; LTCC: L-type (voltage-gated) calcium channel; MyBPC3: Myosin-binding protein-C3 (cardiac); NCX: Na^+/Ca^{2+}-exchanger; NKA: Na^+/K^+-adenosine triphosphatase (sodium pump); P: Phosphorylation; PDE: Phosphodiesterase; PKA: Protein kinase A (cAMP-dependent protein kinase); PLM: Phospholemman; PLN: Phospholamban; R: Regulatory subunit of PKA; RyR2: Ryanodine receptor type 2 (cardiac); SERCA: Sarco(endo)plasmic reticulum calcium adenosine triphosphatase; SR: Sarcoplasmic reticulum. See text for details.