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Caveolae and Caveolins in the Cardiovascular System

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Vesicular Trafficking of Tyrosine Kinase Receptors and Associated Proteins in the Regulation of Signaling and Vascular Function

Compartmentation of Cyclic Nucleotide Signaling in the Heart: The Role of A-Kinase Anchoring Proteins

Trafficking of G Protein–Coupled Receptors

Compartmentation of Cyclic Nucleotide Signaling in the Heart: The Role of Cyclic Nucleotide Phosphodiesterases

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Compartmentation of Cyclic Nucleotide Signaling in the Heart

The Role of Cyclic Nucleotide Phosphodiesterases

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Abstract—A current challenge in cellular signaling is to decipher the complex intracellular spatiotemporal organization that any given cell type has developed to discriminate among different external stimuli acting via a common signaling pathway. This obviously applies to cAMP and cGMP signaling in the heart, where these cyclic nucleotides determine the regulation of cardiac function by many hormones and neuromediators. Recent studies have identified cyclic nucleotide phosphodiesterases as key actors in limiting the spread of cAMP and cGMP, and in shaping and organizing intracellular signaling microdomains. With this new role, phosphodiesterases have been promoted from the rank of a housekeeping attendant to that of an executive officer. (*Circ Res.* 2006;99:816-828.)

Key Words: cAMP ■ cGMP ■ heart ■ G protein–coupled receptor ■ phosphodiesterase

The cyclic nucleotides cyclic adenosine 3',5'-monophosphate (cAMP) and cyclic guanosine 3',5'-monophosphate (cGMP) were identified more than 4 decades ago.^{1,2} Since then, many studies have appeared on how these 2 second messengers are synthesized or degraded, what makes their level go up or down, what they do to target effectors by either covalent (phosphorylation) or noncovalent (direct binding to proteins, such as ion channels or guanine-nucleotide-exchange factors) mechanisms, and how they affect a countless number of cellular functions.^{3–6} In certain tissues and organs, the cyclic nucleotide pathways have been so fully explored over the years that one can

wonder what else is there to be found. This is the case for cAMP in the heart, where it plays a key role in the sympathetic nerve/ β -adrenergic receptor (β -AR)/adenylyl cyclase (AC)/protein kinase A (PKA) axis that serves to stimulate cardiac rhythm (chronotropy) as well as contractile force (inotropy) and relaxation (lusitropy).⁷ Yet, there are a number of questions that have always made us wonder but have only lately begun to receive the attention they deserve: how so many different receptors coupled to cAMP or cGMP signaling pathway manage to achieve specific cellular responses? What is the purpose of the different adenylyl and guanylyl cyclases present in the same cell? Why do

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so many different cyclic nucleotide phosphodiesterases (PDEs) coexist to hydrolyze cAMP and cGMP? Do these cyclic nucleotides and their respective effectors freely diffuse inside the cell or are they localized? Does a cyclic nucleotide compartmentation have any physiological or pathophysiological importance? Some of these questions have received answers in recent studies combining molecular biology, fluorescence imaging, and electrophysiological approaches. In particular, compelling evidence is now accumulating about the formation of molecular complexes (signalosomes) in distinct cellular compartments that influence cyclic nucleotide signaling. Although this review summarizes some of the recent evidence supporting a localized cyclic nucleotide signaling in cardiomyocytes, the reader is encouraged to read other recent reviews on related issues.^{4,5,8–13}

Cyclic AMP Synthesis

Cyclic AMP is synthesized from ATP by at least 9 closely related isoforms of adenylyl cyclases (ACs).^{14,15} In heart, AC5 and AC6 represent the dominant isoforms,¹⁴ although AC7 and AC9 may be present at the mRNA level,^{16,17} and AC4 both at the mRNA and protein level.^{18,19} AC5 and AC6 share strong similarities, both in sequence and functional characteristics: both are activated by G_{α_s} subunits and forskolin and inhibited by G_{α_i} and $G_{\beta\gamma}$ subunits,^{20,21} Ca^{2+} ions,^{22,23} and PKA phosphorylation.^{14,15,20,24,25} However, AC5 and AC6 differ in their regulation by PKC: AC5 is activated,²⁶ whereas AC6 is inhibited,²⁷ by PKC phosphorylation. The lack of specific antibody against each isoform does not allow to examine the specific distribution of AC5 and AC6 at the membrane. However, immunofluorescence staining of isolated adult ventricular myocytes using a common AC5/6 antibody demonstrated a preferential localization of these proteins in T-tubular membranes.^{28,29}

Do AC5 and AC6 play distinct roles in cardiac myocytes? Although, to our knowledge, a dominant negative approach has never been attempted to address that question specifically, several indirect evidence suggest that this is the case. First, AC5 and AC6 show a different pattern of expression during embryonic and postnatal cardiac development, at least at the mRNA level: in rat heart, both isoforms are equally expressed at fetal stage but AC5 mRNA progressively accumulates during ontogenic development, whereas AC6 mRNA remains unchanged.³⁰ Second, AC6 and AC5 expression follows a different pattern of downregulation in several models of heart failure.^{31–33} Finally, studies performed in animal models with a cardiac-directed overexpression of AC5^{34,35} or AC6,^{36–39} or with AC5 inhibition by gene invalidation^{40,41} or specific pharmacological inhibition,^{42,43} suggest that the 2 cyclases exert opposite effects, respectively, beneficial for AC6 and deleterious for AC5, on cardiac cell survival,^{37,43} intracellular Ca^{2+} handling,^{39,41} and contractile function.^{38,41,44} The finding that AC5 and AC6 may have specific roles suggests that the 2 enzymes are located in distinct compartments, interacting with distinct receptors or target proteins. For instance, purinergic and β_1 -adrenergic stimulations differentially activate AC isoforms in rat cardiomyocytes, AC5 being the specific target of the purinergic⁴⁵ and AC6 of the β_1 -adrenergic stimulation.^{46,47} Also, colocalization of AC and K_{ATP} channels was shown to induce a local

regulation of the K_{ATP} channel current by PKA phosphorylation,⁴⁸ or local ATP depletion.⁴⁹

Cyclic GMP Synthesis

Cyclic GMP synthesis is controlled by 2 types of guanylyl cyclases (GCs) that differ in their cellular location and activation by specific ligands: a particulate GC (pGC) present at the plasma membrane, which is activated by natriuretic peptides (NPs) such as atrial (ANP), brain (BNP), and C-type natriuretic peptide (CNP)^{50–52}; and a soluble guanylyl cyclase (sGC) present in the cytosol and activated by nitric oxide (NO).^{52,53} NPs exert their effects by 3 single transmembrane NP receptors: NPR-A, NPR-B, and NPR-C. Both NPR-A and NPR-B have intrinsic GC activity in their cytosolic domain and catalyze the synthesis of cGMP from GTP.⁵⁴ NPR-C lacks enzymatic activity but controls local NP concentrations through constitutive receptor-mediated internalization and degradation⁵⁵ and acts via G_i -dependent mechanisms.⁵⁶ All receptors can be activated by the 3 NPs but NPR-A has a higher affinity for ANP and BNP, whereas NPR-B is more specific for CNP.⁵⁷

Do pGC and sGC play distinct roles in cardiac myocytes? A number of studies clearly support this assumption. For instance, in frog ventricular myocytes, sGC activation causes a pronounced inhibition of L-type Ca^{2+} current (I_{CaL}) on cAMP stimulation,⁵⁸ whereas pGC activation has little effect.⁵⁹ In rabbit atria, pGC activation caused a larger cAMP accumulation (via phosphodiesterase 3 [PDE3] inhibition), cGMP efflux, and ANP release than activation of sGC.⁶⁰ In mouse ventricular myocytes, both pGC and sGC activation exerted similar negative inotropic effects. These effects on cell contraction were mediated by a cGMP-dependent pathway involving cGMP-dependent protein kinase (PKG) and PDEs. However, pGC activation decreased Ca^{2+} transients, whereas sGC activation had marginal effects,⁶¹ similar to what was found in pig airway smooth muscle.⁶² These data suggest that pGC signaling works mainly to decrease intracellular Ca^{2+} level, whereas sGC signaling mainly decreases Ca^{2+} sensitivity. Evidence for different functional effects of cGMP produced by either sGC or pGC also come from studies in noncardiac cell types. For instance, in human endothelial cells from umbilical vein, activation of sGC induces a more efficient relaxation than does pGC activation.⁶³ In airway smooth muscle cells from pig, stimulation of pGC induces relaxation exclusively by decreasing intracellular Ca^{2+} concentration, whereas sGC stimulation decreases both Ca^{2+} concentration and sensitivity of the myofilaments.⁶² In human embryonic kidney, ANP, but not *S*-nitroso-L-acetyl penicillamine (SNAP) (an NO donor) induces a recruitment of PKG to plasma membrane and amplifies GC activity of the NPR-A receptor.⁶⁴

Cyclic Nucleotide Hydrolysis

The level of intracellular cAMP and cGMP is not only regulated by their synthesis but also by their degradation (Figure 1). This is achieved by cyclic nucleotide PDEs, a superfamily of metallophosphohydrolases that specifically cleave the 3',5'-cyclic phosphate moiety of cAMP and/or cGMP to produce the corresponding 5'-nucleotide. In this way, cGMP is converted into 5'-GMP and cAMP into 5'-AMP, hence producing inert molecules, destroying the

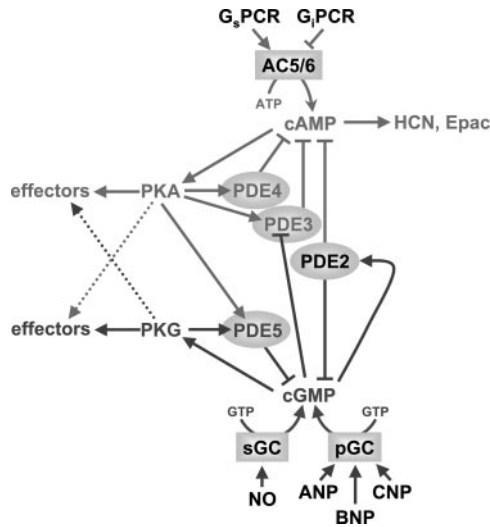


Figure 1. Cyclic AMP and cGMP pathways in cardiac myocytes. The diagram illustrates the enzymes involved in cAMP and cGMP synthesis and degradation and the complex interplay between the 2 signaling pathways in cardiac myocytes (in red for cAMP and in blue for cGMP). This “classical” representation does not account for signaling microdomains.

second messenger activity of cyclic nucleotides, and controlling or limiting the activity of these molecules on their substrates such as PKA, PKG, etc.

PDEs vary in their substrate specificity, mechanism of action and subcellular location.^{65,66} Cardiac PDEs fall into at 5 five families (Figure 1): PDE1, which hydrolyzes both cAMP and cGMP, is activated by Ca^{2+} -calmodulin, and is essentially expressed in a nonmyocyte fraction of cardiac tissue⁶⁷; PDE2, which also can hydrolyze both cAMP and cGMP and is stimulated by cGMP binding to amino terminal allosteric regulatory sites known as GAF domains⁶⁸; PDE3, which has a similar affinity for cAMP and cGMP but a higher V_{max} for the former, making it a cGMP-inhibited cAMP-PDE; PDE4, which is specific for cAMP; and PDE5, which is specific for cGMP. Within these PDE families, multiple isoforms are expressed, either as products of different genes or as products of the same gene through alternative splicing and/or by differential use of translation starting sites. Thus, until now, at least a dozen of different PDE isoforms have been found in heart: PDE1C^{69,70}; PDE2A⁷¹; PDE3A-136, PDE3A-118, and PDE3A-94⁷²; PDE3B⁷³; PDE4B⁷⁴; PDE4D3, PDE4D5, PDE4D8, and PDE4D9⁷⁵; and PDE5A.^{76,77} A last isoform (PDE9A), highly specific of cGMP, has been shown to be expressed at the mRNA level in human⁷⁸ but not mouse heart.⁷⁹ All PDE isoforms but PDE9A^{78,79} are inhibited by xanthine derivatives such as 3-isobutyl-1-methylxanthine (IBMX), and a number of drugs have been developed as selective PDE inhibitors^{65,66}: EHNA⁸⁰ and Bay 60-7550⁸¹ for PDE2; milrinone, cilostamide, and other bipyridines for PDE3⁶⁶; rolipram and Ro 20-1724 for PDE4⁶⁶; sildenafil, tadalafil, and vardenafil for PDE5.^{66,82} These drugs provide valuable pharmacological tools for exploring the functional role of each PDE family in cyclic nucleotide signaling and targeting.

Cyclic AMP and Cyclic GMP Effectors

The cardiac effects of cAMP are classically attributed to PKA-mediated phosphorylation of a myriad of proteins, some

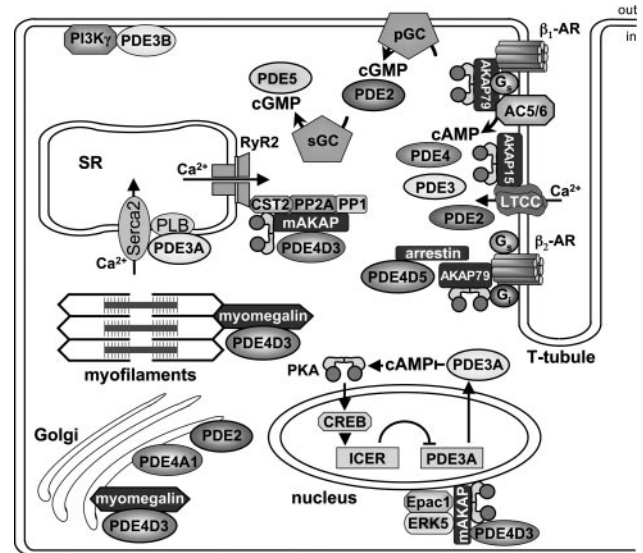


Figure 2. Intracellular distribution of PDE isoforms and macromolecular complexes potentially involving PDE activity in cyclic nucleotide compartmentation in cardiac myocytes.

of which are critically involved in excitation/contraction coupling. These include L-Type Ca^{2+} channels (LTCCs, which underlies the $I_{Ca,L}$),^{83,84} phospholamban (PLB),^{85,86} ryanodine receptor 2 (RyR2),⁸⁷ the phosphatase 1 inhibitor,^{88,89} and a number of contractile proteins, such as troponin I (TnI), and myosin binding protein C.^{7,90} PKA also controls gene expression through the activation of the cAMP response element-binding protein (CREB) family of transcription factors.⁹¹ Cyclic AMP regulates other targets in a PKA-independent manner, like the exchange protein directly activated by cAMP (Epac)^{92,93} and HCN cyclic nucleotide gated ion channels.^{94,95} The consequence of an acute rise in intracellular cAMP concentration is in most cases a positive chronotropic, inotropic, or lusitropic effect, or a combination of 2 or more of these. These effects are counteracted by acetylcholine (ACh) released from sympathetic nerves. ACh binds to muscarinic M2 receptors, which inhibit cAMP synthesis through pertussis toxin-sensitive G_i proteins.⁹⁶

Cyclic GMP is often represented as the mirror of cAMP. In the short term, cGMP usually exerts negative metabolic as well as inotropic effects^{97,98} and opposes most of the positive effects of cAMP on cardiac function.⁹⁹ On NO or NP action, cGMP accumulates and interacts with several targets, such as PKG and PDEs (Figure 1), which attenuate the β -adrenergic response.^{99,100} In the long term, eg, during chronic cGMP pathway stimulation by NO^{101,102} or NPs,^{103,104} or in transgenic mice with cardiac overexpression of endothelial or inducible NO synthases,¹⁰⁵ cGMP possesses antihypertrophic effects.^{106–108}

Compartmentation of Cyclic Nucleotide Signaling

Several observations have suggested that some components within the cyclic nucleotide-signaling pathway are colocalized to discrete regions of the plasma membrane such as caveolae^{109–112} and transverse tubules,^{28,29} thereby allowing rapid and preferential modulation of cAMP and cGMP production within a defined microenvironment (Figure 2).

With the discovery of A-kinase anchoring protein (AKAP),^{113,114} it has become apparent that intracellular targeting of PKA as well as the preassembly of components of signaling pathways in clusters or on scaffolds are important for the speed and organization of cAMP signal transduction events.¹² However, one would wonder how specificity is maintained when small diffusible molecules such as cAMP and cGMP are generated during signaling cascade. Localized cyclic nucleotide signals may be generated by interplay between discrete production sites and restricted diffusion within the cytoplasm. In addition to specialized membrane structures that may circumvent cAMP and cGMP spreading,^{8,115} degradation of these cyclic nucleotides by PDEs appears critical for the formation of dynamic microdomains that confer specificity of the response (Figure 2).^{116–119}

The first evidence for a compartmentation of cAMP signaling in heart comes from experiments made almost 30 years ago in isolated perfused hearts.^{120–122} Important differences were observed when comparing hearts perfused with different agonists activating the cAMP cascade, particularly via β_1 -AR and prostaglandin E₁ receptor (PGE₁-R): with isoproterenol (ISO), cAMP is elevated, the force of contraction is enhanced, soluble and particulate PKA are activated, and the activity of phosphorylase kinase and glycogen phosphorylase is increased; with PGE₁, cAMP content and soluble PKA activity are also increased, but there is no change in contractile activity or in the activities of PKA substrates that regulate glycogen metabolism.^{122,123} Similar results were reproduced in isolated myocytes.¹²⁴ The situation is even more complex if one considers that a given cardiac myocyte expresses many other G_s-coupled receptors, besides β_1 -ARs and PGE₁-Rs, that increase cAMP but produce different effects. For instance, adult rat ventricular myocytes also express β_2 -ARs, glucagon receptors (Glu-Rs), and glucagon-like peptide-1 receptors (GLP₁-Rs). β_2 -AR stimulation increases contractile force but does not activate glycogen phosphorylase¹²⁵ and does not accelerate relaxation^{126,127} (however, see Bartel et al¹²⁵); Glu-R stimulation activates phosphorylase and exerts positive inotropic and lusitropic effects, but the contractile effects fade with time¹²⁸; GLP₁-R stimulation exerts a modest negative inotropic effect despite an increase in total cAMP comparable to that elicited by a β_1 -adrenergic stimulation.¹²⁹

These results clearly show that the cell is able to distinguish between different stimuli acting on a common signaling cascade. One possible way to achieve that distinction is to confine the cyclic nucleotide signaling cascade to distinct intracellular compartments that may differ depending on the stimulus used.

Methods to Study Cyclic Nucleotide Compartmentation in Intact Cardiomyocytes

During 20 years, most of the evidence supporting a compartmentation of cyclic nucleotide signaling in cardiac preparations was gathered using biochemical assays in fractionated dead tissues or cells. However, during the last decade, a number of sophisticated methods have been developed which now allow to evaluate the role of cyclic nucleotide compartmentation in intact living cells.

The first such method combines a classical whole-cell patch-clamp recording of I_{CaL} (as a probe for cAMP/PKA activity) with a double-barreled microperfusion system.¹¹⁶

This allows to test the effect of a local application of a receptor agonist on I_{CaL} in the part of the cell exposed to the agonist and compare it with the response of the Ca²⁺ channels located on the nonexposed part. This method provided the first evidence for a local elevation of cAMP in response to a β_2 -adrenergic stimulation in frog ventricular cells as compared with a uniform elevation of cAMP in response to forskolin, a direct AC activator.¹¹⁶ A similar conclusion was reached using the cell-attached configuration of the patch-clamp technique in mammalian cardiomyocytes¹³⁰ and neurons¹³¹ by applying a β_2 -adrenergic agonist either inside or outside the patch pipette while recording single LTCC activity in the patch of membrane delimited by the pipette.

More direct methods have been developed to monitor cyclic nucleotide changes using fluorescent probes and imaging microscopy. The first such probe was FICRhR, a fluorescent indicator for cAMP that consists of PKA in which the catalytic (C) and regulatory (R) subunits are each labeled with a different fluorescent dye, respectively, fluorescein and rhodamine.¹³² Fluorescence resonance energy transfer (FRET) occurs in the holoenzyme complex R2C2 but when cAMP binds to the R subunits, C subunits dissociate, and the FRET signal is impaired. The change in shape of the fluorescence emission spectrum allows cAMP concentrations to be visualized in real-time in single living cells, as long as it is possible to microinject the cells with the labeled holoenzyme.¹³² This in itself represents a major technical challenge, particularly in cardiomyocytes,¹³³ and has prompted the search for genetically encoded probes. A cAMP probe has been generated using the same principle as FICRhR but by fusing a yellow fluorescent protein (YFP) and a cyan fluorescent protein (CFP) to R and C subunits, respectively.¹³⁴ On a similar principle, through genetic modifications of other target effectors, a number of different probes are now available for real-time measurements of cAMP^{135–138} and cGMP^{139,140} in living cells, including cardiac myocytes.^{74,77,119,141,142}

A third type of approach is based on the use of recombinant cyclic nucleotide-gated channel (CNG) channels as cyclic nucleotide biosensors. The methodology was developed in a series of elegant studies in model cell lines for the measurement of intracellular cAMP.^{115,143,143,144} This method uses wild-type or genetically modified α subunits of rat olfactory CNG channel (CNGB2), which form a cationic channel directly opened by cyclic nucleotides. Adult cardiac myocytes infected with an adenovirus encoding the native or modified channels elicit a nonselective cation current when, respectively, cGMP¹⁴⁵ or cAMP concentration^{146,147} rises beneath the sarcolemmal membrane.

Role of PDEs in Cyclic Nucleotide Compartmentation

Probably the first evidence for a contribution of PDEs to intracellular cyclic nucleotide compartmentation comes from a study in guinea pig perfused hearts.¹⁴⁸ In that study, ISO was shown to significantly increase intracellular cAMP, cardiac contraction and relaxation, as well as phosphorylation of PLB and TnI, whereas the nonselective PDE inhibitor IBMX or the PDE3 inhibitor milrinone enhanced contraction

and relaxation but had little or no effect on phosphorylation of PLB and TnI, despite a relatively large increase in tissue cAMP level.¹⁴⁸ These results were attributed to a functional cellular compartmentation of cAMP and PKA substrates resulting from a different expression of PDEs at the membrane and in the cytosol.¹⁴⁹ Many subsequent studies have examined the degree of accumulation of cAMP or activation of cAMP dependent phosphorylation in particulate and soluble fractions of cardiac myocytes. In an elegant such study performed in canine ventricular myocytes, Hohl and Li demonstrated that cytosolic and particulate pools of cAMP are differently affected by various treatments designed to raise intracellular cAMP.¹⁵⁰ These authors have demonstrated that approximately 45% of the total cAMP is found in the particulate fraction in response to ISO, but this fraction declined to <20% when IBMX was added to ISO, although total cAMP still increased approximately 3-fold. This suggests that cAMP-specific PDE activity resides predominantly in the cytosolic compartment and is responsible for the particulate cAMP microdomains generation that cause Ca²⁺ mobilization and cardiac inotropic state through particulate PKA activation and phosphorylation of membrane and contractile proteins. Even if the cell is able to generate and accumulate cAMP that exceeds what is needed for a maximal physiologic response under PDE inhibition and forskolin stimulation, only particulate cAMP content determines the physiological response. These results show that PDEs maintain the specificity of the β -adrenergic response by limiting the amount of cAMP diffusing from membrane to cytosol.

These biochemical data are in full agreement with functional studies in frog ventricular myocytes, where the effect of a local application of ISO on $I_{Ca,L}$ was tested in the presence or absence of IBMX.¹¹⁶ Although the $I_{Ca,L}$ response to ISO was much higher at the side of ISO application than in the nonexposed part of the cell, complete PDE inhibition in the presence of ISO released the cAMP signal to activate LTCCs in the remote part of the cell. Thus, these results suggest that PDE activity contributes to generate cAMP microdomains involved in the β -adrenergic stimulation of Ca²⁺ channels. A recent study using recombinant CNG channels demonstrates that this also applies to other G_s-coupled receptors (β_1 -AR, β_2 -AR, PGE1-R, Glu-R), with a specific pattern of PDE activity determining the specificity of the cAMP signals generated by each receptor (Figure 3).¹⁴⁷ For instance, cAMP elicited by β_1 -AR is regulated by PDE3 and by PDE4, whereas cAMP signal generated by Glu-R is exclusively regulated by PDE4. In mouse neonatal cardiomyocytes, PDE4D was shown to selectively impact cAMP signaling by β_2 -AR, while having little or no effect on β_1 -AR signaling.¹⁵¹ Indeed, although β_2 -AR activation leads to an increase in cAMP production, the cAMP generated does not have access to the PKA-dependent signaling pathways by which the β_1 -AR regulates the contraction rate, unless PDE4D is inhibited or its gene has been invalidated.¹⁵¹

The use of selective inhibitors of the dominant cardiac PDE isoforms has allowed to evaluate the contribution of 4 different PDE families in the compartmentation of cAMP and cGMP pathways in cardiac myocytes: PDE2, PDE3, PDE4, and PDE5. Coimmunoprecipitation experiments have further

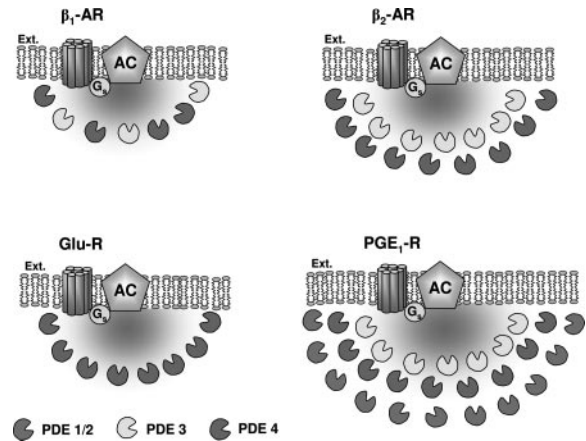


Figure 3. PDE-dependent cAMP compartmentation. Activation of different G_s-coupled receptors leads to AC activation and cAMP production in different compartments delimited by different subsets of PDE isoforms. (For more details, see Rochais et al.¹⁴⁶)

demonstrated that macromolecular complexes exist at different locations within a cardiac myocyte that include PDE3 and PDE4 isoforms, forming local signaling microdomains (Figures 2 and 3). The role of each individual PDE family in these microdomains is reviewed below.

Phosphodiesterase 2

Cyclic GMP-stimulated PDE (PDE2) hydrolyzes both cAMP and cGMP with low affinity. A single PDE2 variant, PDE2A, is expressed in cardiac tissues and in isolated cardiomyocytes of several species, including rat, bovine, and human.^{152–154} PDE2 is found both in the cytosol and associated to functional membrane structures (plasma membrane, sarcoplasmic reticulum [SR], Golgi, nuclear envelope).⁶⁵ Although PDE2 activity is relatively small compared with other cardiac PDEs, such as PDE3 and PDE4, its presence at the plasma membrane contributes to regulate the activity of cardiac LTCCs when cGMP level is increased.⁹⁹ This was first demonstrated in frog ventricular myocytes dialyzed with cAMP and cGMP, where PDE2 is able to hydrolyze cAMP and hence reduce $I_{Ca,L}$ on application of cGMP, even when >5 μ mol/L cAMP is continuously dialyzed inside the cell via the patch pipette.^{155,156} Increased knowledge of the contribution of PDE2 to cardiac function has accumulated after the demonstration that the adenosine deaminase inhibitor erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA) behaves as a selective PDE2 inhibitor.^{80,157} EHNA reverses the inhibitory effect of high concentrations of cGMP or NO donors on $I_{Ca,L}$ in frog ventricular^{80,158} and human atrial myocytes.^{159,160} EHNA alone stimulates basal $I_{Ca,L}$ in isolated human atrial myocytes,¹⁶¹ indicating a possible role of basal guanylyl cyclase activity in these cells.

The role of PDE2 in cyclic nucleotide compartmentation was first examined in frog cardiac myocytes, using the double-barreled microperfusion technique and local applications of NO donors and/or EHNA on $I_{Ca,L}$ stimulated by ISO.¹⁵⁸ The results of that study demonstrated that local stimulation of soluble guanylyl cyclase by NO leads to a strong local depletion of cAMP near the LTCCs caused by

activation of PDE2 but only to a modest reduction of cAMP in the rest of the cell. This may be explained by the existence of a tight microdomain among β -ARs, LTCC, and PDE2 (Figure 2).¹⁵⁸ A similar conclusion was reached recently in rat neonatal cardiomyocytes, using the FRET-based imaging technique.¹⁴²

PDE2 is not only involved in the control of subsarcolemmal cAMP concentration but also controls the concentration of cGMP in that compartment. Indeed, a recent study performed in adult rat ventricular myocytes using the CNG technique compared the effects of activators of pGC (using ANP or BNP) and sGC (using NO donors) on subsarcolemmal cGMP signals and the contribution of PDE isoforms to these signals.¹⁴⁵ The main result of that study is that the “particulate” cGMP pool is readily accessible at the plasma membrane, whereas the “soluble” pool is not, and that the particulate pool is under the exclusive control of PDE2 (Figure 2).¹⁴⁵ Therefore, differential spatiotemporal distributions of cGMP may contribute to the specific effects of natriuretic peptides and NO donors on cardiac function.

Phosphodiesterase 3

Cyclic GMP inhibition of PDE3 can lead to cAMP increase and to activation of cardiac function.¹⁶² This mechanism accounts for the stimulatory effect of low concentrations of NO donors or cGMP on $I_{Ca,L}$ in human atrial myocytes.^{159,160} However, a recent study performed in perfused beating rabbit atria demonstrated that, depending on whether cGMP is produced by pGC or sGC, the effects on cAMP levels, atrial dynamics, and myocyte ANP release are different, although in both cases the effects are attributable to PDE3 inhibition.⁶⁰ These results suggest that cGMP/PDE3/cAMP signaling produced by pGC and sGC is compartmentalized.⁶⁰ The role of PDE3 in cyclic nucleotide compartmentation likely depends on its intracellular distribution. PDE3 is present in both cytosolic and membrane fractions of cardiac myocytes, with important species and tissue differences.^{65,163} For instance, in dog heart, all PDE3 activity revealed in the membrane fraction appears to be associated with the SR membrane.¹⁶⁴ Inhibition of PDE3 under such conditions could lead to localized increases in cAMP and PKA pools, leading to increased PLB phosphorylation (Figure 2).

Three isoforms of PDE3 have been identified in human myocardium.⁷² They appear to be generated from PDE3A gene and localize to different intracellular compartments: PDE3A-136 is present exclusively in microsomal fractions, whereas PDE3A-118 and PDE3A-94 are both present in microsomal and cytosolic fractions.¹⁶⁵ The presence of different PDE3A isoforms in cytosolic and microsomal fractions of cardiac myocytes is especially interesting in view of the facts that cAMP metabolism in these compartments can be regulated in an independent manner and that changes in cAMP content in these compartments correlate with changes of different physiological parameters, such as intracellular Ca^{2+} homeostasis and contractility.^{110,166} These observations are relevant in a physiological context because competitive inhibitors of PDE3 confer short-term hemodynamic benefits but adversely affect long term survival in dilated cardiomyopathy.^{167,168} This biphasic response is likely to result from an increase in the phosphorylation of a large number of PKA

substrates, some of which may contribute to the beneficial effects (phosphorylation of PLB), whereas others contribute to the adverse effects (phosphorylation of LTCC, RyR2, and CREB). If one would suppose that different isoforms regulate different proteins in response to different signals, logically agents capable of selectively activating or inhibiting individual PDE3A isoforms may have advantages over currently available nonselective PDE3 inhibitors in therapeutic applications. For instance, an agent that selectively inhibits SR-associated PDE3A-136 might preserve intracellular Ca^{2+} cycling and contractility in patients taking β -AR antagonists, without concomitant arrhythmogenic effects.^{72,168}

Another mechanism that may participate in the detrimental effect of PDE3 inhibitors on cardiac function is apoptosis.¹⁶⁹ PDE3A is downregulated in heart failure,¹⁷⁰ and this leads to the induction of the proapoptotic transcriptional repressor ICER (Inducible Cyclic AMP Early Repressor) in a CREB-dependent manner (Figure 2).¹⁶⁹ Elevated ICER represses antiapoptotic proteins such as Bcl-2 and the PDE3A gene itself, thus creating a positive feedback loop that maintains reduced PDE3A levels and elevated ICER levels.¹⁷¹ Interestingly, PDE4 inhibition does not modulate CREB and ICER, and is not proapoptotic, thus providing another example of cAMP compartmentation in cardiomyocytes.¹⁶⁹

In addition to PDE3A, cardiac myocytes also express a PDE3B isoform, at least in mouse.⁷³ Of particular interest is the finding that this isoform forms a complex at the cardiac sarcolemmal membrane with the G-protein coupled, receptor-activated phosphoinositide 3-kinase γ (PI3K γ) (Figure 2).⁷³ Ablation of PI3K γ in mice (PI3K $\gamma^{-/-}$) induces an exacerbated heart failure in response to aortic constriction, which appears to be attributable to a PDE3B inhibition and to an excess of cAMP. But mice carrying a targeted mutation in the PI3K γ gene causing loss of kinase activity (PI3K $\gamma^{KD/KD}$) exhibit normal cardiac contractility associated with normal cAMP levels after aortic stenosis compared with PI3K $\gamma^{-/-}$. Therefore, PI3K γ does not activate PDE3B via its kinase activity, but rather serves as an anchoring protein, which recruits PDE3B into a membrane compartment, where cAMP homeostasis shapes the chronic sympathetic drive.⁷³

Phosphodiesterase 4

The PDE4 family is encoded by 4 genes (A, B, C, and D) that generate approximately 20 different isoforms, each of which is characterized by a unique N-terminal region.^{172,173} Transcripts for PDE4A, PDE4B, and PDE4D isoforms were found in rat heart.^{69,74,75,154} In the PDE4D family, mRNA for PDE4D1, PDE4D2, PDE4D3, PDE4D5, PDE4D7, PDE4D8, and PDE4D9 is present in rat heart,^{69,75} but only PDE4D3, PDE4D5, PDE4D8, and PDE4D9 are expressed as proteins and active enzymes.⁷⁵

An emerging theme in PDE4 action is that individual isoforms appear to be restricted to defined intracellular microenvironments, thus regulating particular sets of intracellular processes (Figure 2).^{12,173–175} Compartmentation of PDE4 isoforms is mediated by their unique N-terminal domains, which provide the “postcode” for cellular localization.¹¹ For instance, PDE4A1 contains a lipid-binding domain, TAPAS, with specificity for phosphatidic acid that

serves to target this PDE to specific cellular membranes.¹⁷⁶ In the heart, PDE4D3 is targeted to sarcomeric region of cardiomyocytes through binding to an anchor protein called myomegalin,¹⁷⁷ and to the perinuclear region through binding to muscle AKAP (mAKAP).¹⁷⁸ This latter complex is interesting because mAKAP not only binds PKA and PDE4D3 but also Epac1 and extracellular signal-regulated kinase 5 (ERK5).¹⁷⁹ The 3 functionally distinct cAMP-dependent enzymes contained in this macromolecular complex (PKA, PDE4D3, and Epac1) respond to cAMP in different ranges of concentrations: PKA responds to nanomolar concentrations and would become activated early; PDE4D3 (K_m , 1 to 4 $\mu\text{mol/L}$), and Epac1 (K_d 4 $\mu\text{mol/L}$) would become activated once cAMP concentrations reached micromolar levels. Conversely, inactivation of PDE4D3 and Epac1 would precede PKA holoenzyme reformation as cAMP levels decline.¹⁷⁹ Besides, phosphorylation of PDE4D3 by PKA on Ser54 enhances its activity^{75,173} and on Ser13 increases its affinity to mAKAP,¹⁸⁰ whereas phosphorylation by ERK5 on Ser579 suppresses its activity.¹⁷⁹ Therefore, when Epac1 is activated by cAMP, it mobilizes Rap1, which suppresses ERK5 activation and relieves the inhibition of PDE4D3. With such fine tuning, this complex provides spatial control of PKA signaling by mAKAP anchoring and temporal control and termination of the cAMP signaling event by PDE activity in the immediate vicinity.^{174,178} This compartment of cAMP signaling in the perinuclear region may control the release of C subunit into the nucleus^{178,181} and hence gene regulation.¹⁷⁴

The same PDE4D3 was also found recently to be an integral component of the RyR2/ Ca^{2+} -release channel complex at the SR membrane (Figure 2).¹⁸² In addition to RyR2 and PDE4D3, this complex is composed of mAKAP, PKA, FKBP12.6 (calstabin2, a negative modulator or channel-stabilizing subunit of RyR2), and the protein phosphatases PP1 and PP2A.^{183,184} PKA phosphorylation of Ser2809 on RyR2 increases the open probability of the Ca^{2+} -release channel and decreases the binding affinity for the channel-stabilizing subunit calstabin2, contributing to SR Ca^{2+} store depletion.¹⁸⁴ Of particular interest is the observation that heart failure in patients and animal models is accompanied by PKA hyperphosphorylation of RyR2, which makes RyR2 channels "leaky," hence promoting cardiac dysfunction and arrhythmias.¹⁸⁴ Two sets of evidence indicate that this is attributable to a reduction in PDE4D3 activity in the RyR2 complex¹⁸²: first, PDE4D3 levels in the RyR2 complex appear reduced in failing human hearts¹⁸²; second, genetic inactivation of PDE4D in mice is associated with a cardiac phenotype comprised of a progressive, age-related cardiomyopathy, and exercise-induced arrhythmias, despite normal global cAMP signaling.¹⁸² These results emphasize the importance of cAMP signaling microdomains and point to the intriguing possibility that deregulation of specific compartments may lead to a disease state.

A final example of a complex around a PDE4 isoform in heart is that formed by PDE4D5 and β -arrestins (Figure 2).¹⁸⁵ β -Arrestins are scaffold proteins that initiate desensitization of β_2 -AR (as well as several other G protein-coupled receptors) by translocating from the cytosol to the plasma membrane, where they directly bind the activated receptors.

Recent studies have shown that β -arrestins can form stable complexes with all 4 PDE4 subfamilies in cytosol¹⁸⁵ but that PDE4D5 possesses a unique amino-terminal region that confers preferential interaction with β -arrestins.^{11,175,186,187} The specific role of this PDE4D5/ β -arrestin interaction in the β_2 -AR signaling cascade comes from a unique feature of this particular receptor, which can couple to both G_s and G_i .¹⁸⁸ On agonist challenge, β_2 -AR couples to G_s that activates AC, thereby elevating local cAMP concentration and activating membrane PKA anchored to AKAP-79.¹⁸⁷ PKA in turn phosphorylates the β_2 -AR, which triggers a shift in its coupling from G_s to G_i , hence activating ERK through a Src-regulated pathway.¹⁸⁹ Therefore, recruitment by the activated β_2 -AR of the PDE4D5/ β -arrestin puts a brake in the PKA phosphorylation of the receptor, and prevents its shift to G_i -signaling cascade; conversely, disruption of this complex enhances PKA phosphorylation of the β_2 -AR, leading to a dramatic change in its function.^{189,190}

Phosphodiesterase 5

PDE5 is highly expressed in vascular smooth muscle, and its inhibition is a primary target for the treatment of erectile dysfunction and pulmonary hypertension.^{82,191} Although the contribution of PDE5 to the regulation of cardiac function is a matter of debate,^{70,98,192} there is evidence for PDE5 expression in cardiac myocytes, both at the mRNA¹⁹³ and protein level.^{76,77} Recently, PDE5 inhibition using sildenafil (Viagra) was shown to decrease the β -adrenergic stimulation of cardiac systolic and diastolic function in dog,⁷⁶ mouse,⁷⁷ and human^{98,194} as well as the β -stimulation of $I_{\text{Ca,L}}$ in guinea pig ventricular myocytes.¹⁹⁵ In mouse ventricular myocytes, sildenafil was shown to inhibit apoptosis¹⁹⁶ and to reduce infarct size following ischemia/reperfusion in the myocardium.¹⁹⁷ Moreover, chronic exposure to sildenafil was found to prevent and reverse cardiac hypertrophy in mouse hearts exposed to sustained pressure overload.¹⁹⁸ Most recently, PDE5 was also shown to contribute to intracellular cGMP compartmentation in cardiac myocytes (Figure 2).¹⁴⁵ Indeed, using the recombinant CNG channel approach to measure subsarcolemmal cGMP concentration in adult rat ventricular myocytes, sildenafil produced a dose-dependent increase of the CNG current activated by NO donors but had no effect on the current elicited by ANP. Therefore, PDE5 exerts a specific spatiotemporal control on the pool of intracellular cGMP synthesized by sGC but not that generated by pGC, which, as discussed above, is under the exclusive control of PDE2.¹⁴⁵ This could be either because PDE5 is more closely compartmentalized with sGC than pGC (Figure 2), or because PKG, which activates PDE5,⁸² is compartmentalized with sGC but not pGC. Therefore, differential spatiotemporal distributions of cGMP may contribute to the specific effects of NPs and NO donors on cardiac function.⁵⁸ Inasmuch as these results apply to vascular smooth muscle, they may help to explain why sildenafil and other PDE5 inhibitors are contraindicated in men who use nitrate medications.^{59–61,199,200}

Cooperative Role of PDE Isoforms

In many examples, more than 1 PDE isoform is involved in controlling the cAMP or cGMP concentration at any given

intracellular location inside a cardiomyocyte. For instance, in the case of cGMP, both PDE2 and PDE5 were found to control the subsarcolemmal concentration of cGMP on activation of sGC by NO donors in rat cardiomyocytes as demonstrated by selective inhibition of each PDE isoform. Indeed, EHNA or sildenafil used alone raised subsarcolemmal cGMP to a lower level as when the 2 inhibitors were applied together or when both PDEs were blocked by IBMX.¹⁴⁵ Similarly, the activity of cardiac LTCCs or the force of contraction is affected by the hydrolytic activity of several PDEs, because inhibition of a single PDE isoform is insufficient to raise cAMP level enough to activate these parameters.^{154,201,202} Real-time measurements of cAMP in isolated cardiomyocytes using either the FRET-based or the recombinant CNG channel method have shown that PDE4 and to a lesser extent PDE3 regulate the amplitude of cAMP response on a β -adrenergic stimulation.^{74,146} The more prominent role of PDE4 versus PDE3 families may partly result from a larger stimulatory effect of PKA phosphorylation on the former, providing a faster negative feedback regulation on cAMP concentration (Figure 1).^{65,70,74,146,203,204} Indeed, blockade of PKA strongly increased the cAMP signal at the membrane on β -AR stimulation of adult rat ventricular myocytes.¹⁴⁶

Restore Cyclic Nucleotide Compartments in Heart Failure? “Act Locally, Think Globally”

Although an acute stimulation of the cAMP pathway is beneficial for the heart, a sustained activation, as occurs for instance in transgenic mice with cardiac overexpression of β_1 -ARs,²⁰⁵ G_s ,²⁰⁶ or PKA,²⁰⁷ leads to hypertrophic growth, ventricular dysfunction and, ultimately, to heart failure.^{168,208} A similar situation is found in different forms of human chronic heart failure, which are all associated with elevated catecholamines.^{184,209,210} A possible explanation for the “good” acute and “bad” chronic effects of cAMP may reside in the capacity of the cell to maintain proper cAMP signaling microdomains. That capacity may be overwhelmed in a chronic setting, resulting in a global and deleterious rise in cAMP.

Can we thus imagine restoring cAMP compartments and rescuing or preventing the “bad” outcomes of cAMP elevation, for instance, via local and isoform-specific PDE activation? Recent studies performed on a transgenic mouse line (AC8TG) provide some support for this paradigm. In this animal model, the human neuronal type 8 AC (AC8) protein was specifically expressed in cardiomyocytes, leading to a 7- and 4-fold increase in total AC and PKA activity, respectively.²¹¹ Unlike the endogenous cardiac AC5 and AC6 isoforms, which are inhibited by Ca^{2+} , AC8 is activated by Ca^{2+} /calmodulin.²¹² Therefore, one would expect that at each heart beat, Ca^{2+} influx through LTCCs or Ca^{2+} release via RyR2 would activate AC8, hence creating a positive feedback via PKA on both $I_{Ca,L}$ and RyR2, which might cause a detrimental Ca^{2+} overload. Yet, AC8TG mice show no sign of hypertrophy or cardiomyopathy at up to 3 months of age.^{211,213} When examined at the organ level, isolated perfused hearts from AC8TG mice show an increased heart rate, larger amplitude of contraction, faster kinetics of contraction and relaxation as compared with nontransgenic (NTG) mice.²¹³ At

the single cell level, myocytes from AC8TG hearts contract faster and stronger, develop larger and faster Ca^{2+} transients, which represent the hallmarks of an improved SR function.²¹³ Therefore, cardiomyocytes from AC8TG mice respond positively to the enhanced cAMP synthesis by an improved SR function, similarly to an acute β -adrenergic stimulation. But why do the myocytes not develop Ca^{2+} overload as would be expected from the continuous stimulation of the cAMP/PKA pathway? Patch-clamp experiments revealed that basal $I_{Ca,L}$ amplitude was not different in ventricular myocytes isolated from AC8TG and NTG hearts, indicating that LTCCs in AC8TG mice were protected from the large amount of cAMP generated by AC8.²¹³ Surprisingly, on PDE inhibition by IBMX, a 2-fold larger increase in $I_{Ca,L}$ was observed in AC8TG versus NTG hearts, indicating that cardiac expression of AC8 is accompanied by a strong compartmentation of the cAMP signal attributable to PDE activity that shields LTCCs and protects the cardiomyocytes from Ca^{2+} overload.²¹³ Additional biochemical experiments confirmed an increase in cAMP/PDE activity and a rearrangement of PDE isoforms in AC8TG versus NTG hearts.²¹⁴ Therefore, through enhanced PDE activity and compartmentation, the AC8TG mouse model provides a nice example where chronic activation of cAMP pathway only makes the “good,” not the “evil.” As discussed above, another such example can be found in animal models with a cardiac-directed overexpression of AC6.^{36–39}

The concept that cardiac cAMP signaling can produce both “good” and “bad” effects depending on where within the cell it is being activated is certainly relevant to all forms of heart failure, where major alterations in cAMP signaling occur. The evidences reviewed here demonstrate that physiological cAMP and cGMP signaling is confined in specific subcellular domains attributable to local activities of specific PDEs. We believe that the “good” outcomes, at least for cAMP, require a strict localized control of the cyclic nucleotide signaling, leading to activation of only a limited number of substrates; the “bad” outcomes occur when compartments are disorganized, a situation likely to exist during the morphological rearrangements that accompany hypertrophy and heart failure. Therefore, an in-depth analysis of cyclic nucleotide signaling in pathologic hypertrophy and heart failure may provide new treatments of heart failure acting on localized cyclic nucleotide signaling to improve heart function and clinical outcomes. Activating specific PDEs in specific compartments, such as PDE4D near RyR2 or PDE2 near LTCCs, or inhibiting other PDEs in other compartments, such as PDE3A or PDE5 near PLB, may help to restore a normal cyclic nucleotide signaling and provide new therapeutic strategies against heart failure.^{103,104,215}

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None.

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