Combination Therapy with β-Adrenergic Receptor Antagonists and Phosphodiesterase Inhibitors for Chronic Heart Failure

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Rational use of phosphodiesterase inhibitors represents an ongoing controversy in contemporary pharmacotherapy for heart failure. In randomized clinical trials, phosphodiesterase inhibitors increased cardiac output at the expense of worsening the rates of sudden cardiac death and cardiovascular mortality. Preliminary findings from ongoing clinical and preclinical investigations of phosphodiesterase activity suggest that combined use of phosphodiesterase inhibitors with β-adrenergic antagonists may prevent these adverse outcomes. Compartmentation of cyclic adenosine 3′,5′-monophosphate signaling may prove critical in determining myocardial response to combination therapy.

Key Words: β-adrenergic receptor antagonist, β-blocker, phosphodiesterase inhibitor, compartmentation, chronic heart failure.

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OUTLINE

The advent of phosphodiesterase inhibition in heart failure was met with early optimism due to a novel mechanism of inotropic action and symptomatic improvement in patients with heart failure.[1–4] Subsequent larger clinical trials, however, noted a consistent increase in mortality among patients receiving oral phosphodiesterase inhibitors, primarily due to sudden cardiac death and cardiovascular mortality.[5–8] These negative findings reduced the clinical role of phosphodiesterase inhibitors to use in patients with acute decompensated heart failure requiring short-term or palliative inotropic support. It is significant to note, however, that early phosphodiesterase inhibitor trials occurred before the benefits of β-adrenergic receptor antagonists in heart failure were widely established. As β-adrenergic receptor antagonists exert a significant protective effect on heart failure mortality, sudden cardiac death, and proarrhythmia (principal adverse events in phosphodiesterase inhibitor trials), the addition of β-adrenergic receptor antagonists to phosphodiesterase inhibitors may constitute a valuable contribution to heart failure pharmacotherapy.

We examine the evidence, both clinical and preclinical, for the combined use of β-adrenergic receptor antagonists and phosphodiesterase inhibitors in patients with heart failure.

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Although the combined use of an inotropic agent with a β-adrenergic receptor antagonist may seem counterintuitive, we also highlight the distinct, complementary pharmacology of these agents and propose a mechanism by which their combination may produce myocardial responses not attainable with either agent alone.

Heart Failure Pathophysiology

Much of the pathophysiology of heart failure stems from longstanding overactivation of the sympathetic nervous system and renin-angiotensin-aldosterone system.[9–11] Elevated concentrations of norepinephrine and angiotensin II produce acute increases in cardiac output, but also cause vasoconstriction, fluid retention, and increased myocardial oxygen demand.[12, 13] Conversely, long-term exposure to elevated concentrations of norepinephrine and angiotensin II promotes myocardial inflammation, hypertrophy, apoptosis, and pathologic remodeling of the myocardium.[9–11] Contemporary pharmacotherapy for heart failure is designed to interrupt sympathetic activity through use of β-adrenergic receptor antagonists[14–18] and to interrupt the renin-angiotensin activity through the use of angiotensin-converting enzyme (ACE) inhibitors,[19–21] angiotensin II receptor blockers,[22, 23] and aldosterone antagonists.[24, 25] These strategies work particularly well in combination.[26]

Role of β_1-Adrenergic Receptor Signaling in Heart Failure

The chronotropic and inotropic effects of norepinephrine result from activation of β_1-adrenergic receptors within the myocardium.[27–29] Norepinephrine binding to the extracellular domain of the β_1-adrenergic receptor induces a conformational change in the cytoplasmic domain of the β_1-adrenergic receptor coupled to a regulatory G-protein. Activation of the G-protein releases a stimulatory α-subunit ($G_{\alpha s}$), which migrates through the sarcolemmal membrane to activate adenylate cyclase, which, in turn, catalyzes cytoplasmic hydrolysis of adenosine 5′-triphosphate (ATP) to cyclic adenosine 3′,5′-monophosphate (cAMP; Figure 1).[28–30]

The cAMP generated by adenylate cyclase floods local regions of the cytoplasm to activate protein kinase A (PKA), which propagates the norepinephrine signal through phosphorylation

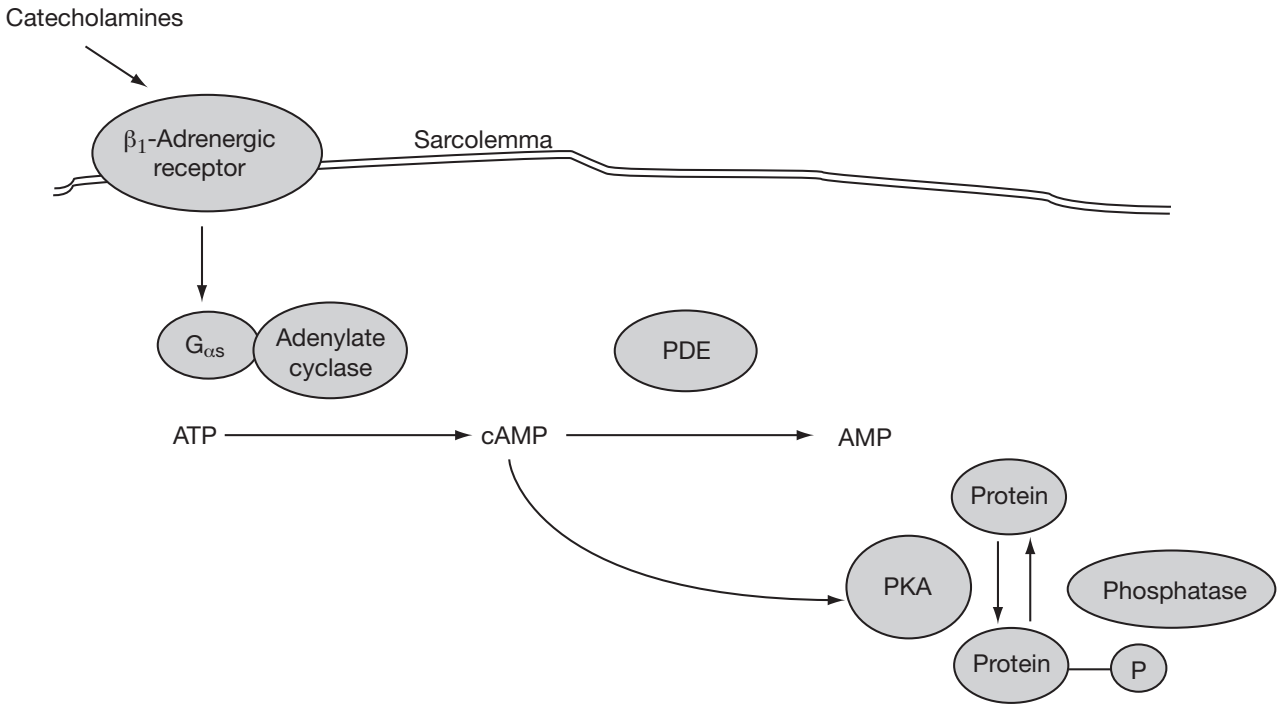

Figure 1. Signaling mediated by cyclic adenosine 3′,5′-monophosphate (cAMP) in cardiac myocytes. AMP = adenosine 5′-monophosphate; ATP = adenosine 5′-triphosphate; $G_{\alpha s}$ = stimulatory α-subunit released by the G protein; P = phosphate; PDE = phosphodiesterase; PKA = protein kinase A. (Adapted from reference 30.)

of multiple cytoplasmic targets. Phosphorylation of PKA targets largely accounts for the acute increases in inotropy and chronotropy associated with norepinephrine administration.[30] Among the many targets of PKA phosphorylation are L-type calcium ion (Ca^{2+}) channels in the plasma membrane to increase Ca^{2+} influx during systole,[31, 32] ryanodine Ca^{2+} channels on the sarcoplasmic reticulum to increase Ca^{2+} release during systole,[33] phospholamban proteins on the sarcoplasmic reticulum to increase calcium resequestration into the sarcoplasmic reticulum during diastole,[34, 35] phosphorylase kinase to stimulate glucose mobilization and glycogen hydrolysis,[36, 37] troponin proteins to regulate actin-myosin interaction during systole,[38, 39] and cAMP response element-binding protein (CREB) to regulate gene expression (Figure 2).[40, 41]

The pathologic effects of norepinephrine in heart failure may be traceable to overactivity of adenylate cyclase, cAMP, and the resultant overphosphorylation of specific PKA targets.[30, 42] Although some of these PKA targets must invariably be responsible for negative heart failure outcomes, other PKA targets may produce their intended effects without contributing to negative heart failure outcomes. For example, CREB is a transcription factor that regulates gene expression upon phosphorylation by PKA. Transgenic animal models with no CREB activity exhibit accelerated myocardial apoptosis and hypertrophy, suggesting a protective effect of CREB phosphorylation.[40, 43] Phospholamban phosphorylation by PKA increases activity of ATP-driven pumps to resequester Ca^{2+} in the sarcoplasmic reticulum. Animal models that mimic hyperphosphorylation of phospholamban demonstrate improved contractility and reduced

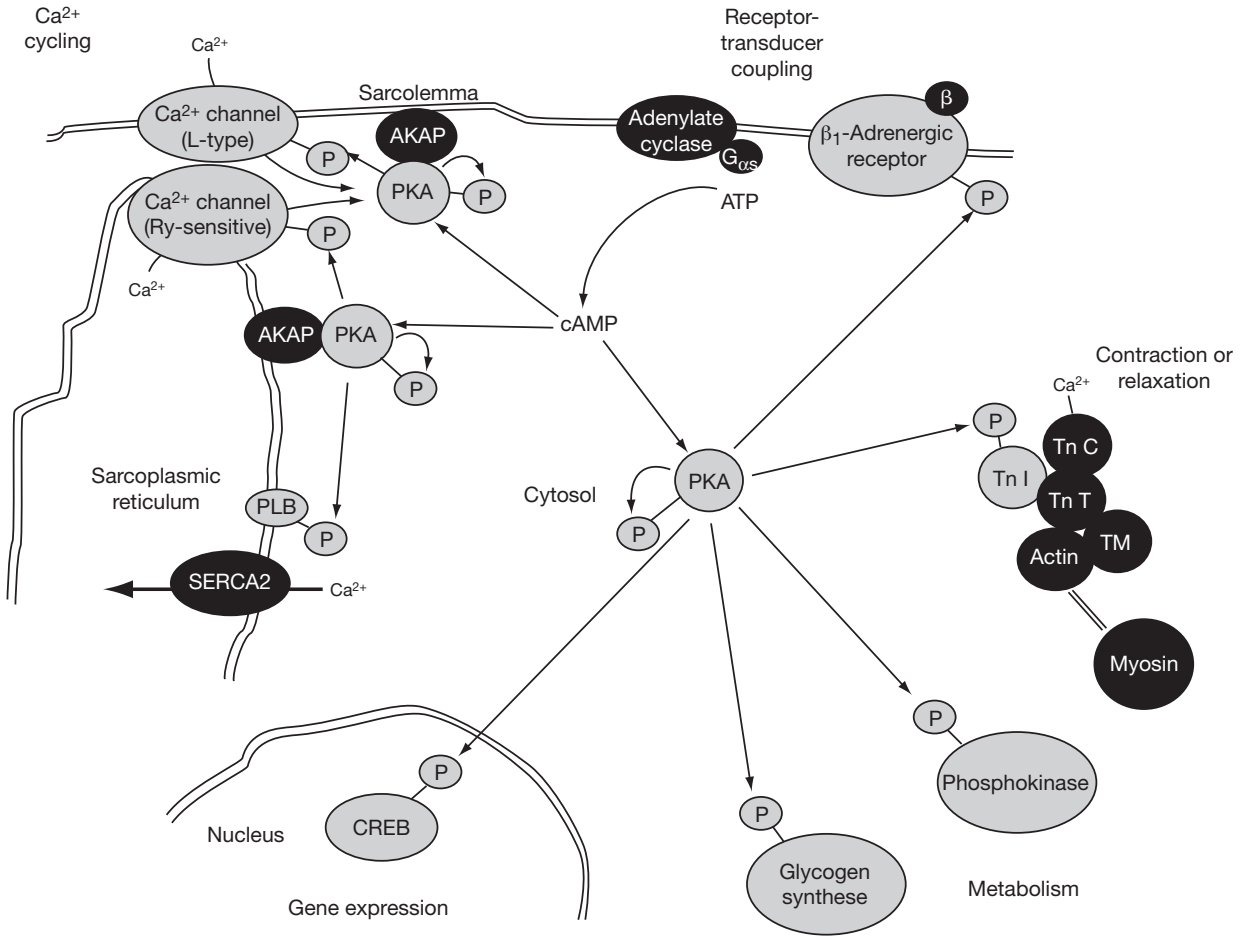

Figure 2. Actions of cyclic adenosine 3′,5′-monophosphate (cAMP) in cardiac myocytes. AKAP = A kinase anchoring protein; ATP = adenosine 5′-triphosphate; Ca^{2+} = calcium ion; CREB = cAMP response element-binding protein; $G_{\alpha s}$ = stimulatory α-subunit released by the G protein; P = phosphate; PLB = phospholamban; PKA = protein kinase A; Ry = ryanodine; SERCA2 = sarco-endoplasmic reticulum Ca^{2+}–ATPase; TM = tropomyosin; Tn = troponin. (Adapted from reference 41.)

development of heart failure symptoms.[34, 35, 44]

Unfortunately, there is little possibility of activating select PKA targets with β-adrenergic receptor antagonists alone. All β-adrenergic receptor antagonists (regardless of β_1 or β_2 selectivity) reduce cAMP production downstream from the β-adrenergic receptor and, therefore, nonspecifically reduce phosphorylation of the associated PKA targets. In simpler terms, β-adrenergic receptor antagonists produce "blanket" inhibition of all associated PKA targets (i.e., activating none of them). Although clinical trial data with β-adrenergic receptor antagonists support the generalized benefit of this blanket PKA inhibition, as few as 40% of patients experience clinical improvement with β-adrenergic receptor antagonist treatment.[16, 45, 46] This incomplete response may be due, in part, to nonselective reduction of PKA activity that masks the potential benefits of individual PKA targets. To investigate the potential benefits of PKA selectivity, a second class of drugs must be used to activate individual PKA targets in the presence of β_1-adrenergic receptor blockade. Phosphodiesterase inhibitors may provide such an opportunity.

Role of Phosphodiesterases in β_1-Adrenergic Receptor Signaling

Under normal physiologic conditions, the norepinephrine signal is counterregulated within the cytoplasm by phosphodiesterase enzymes, which catalyze the breakdown of cAMP to inactive AMP.[47, 48] Phosphodiesterase activity lowers cAMP concentration, reduces PKA activity, and thereby interrupts the norepinephrine signal. Conversely, phosphodiesterase inhibition reduces cAMP degradation, increases phosphorylation of PKA targets, and thereby perpetuates the norepinephrine signal. This augmented cAMP and PKA activity produces the clinically observed inotropy of phosphodiesterase inhibitors in patients with acute decompensated heart failure.[48] It is significant to note that the inotropic mechanism of phosphodiesterase

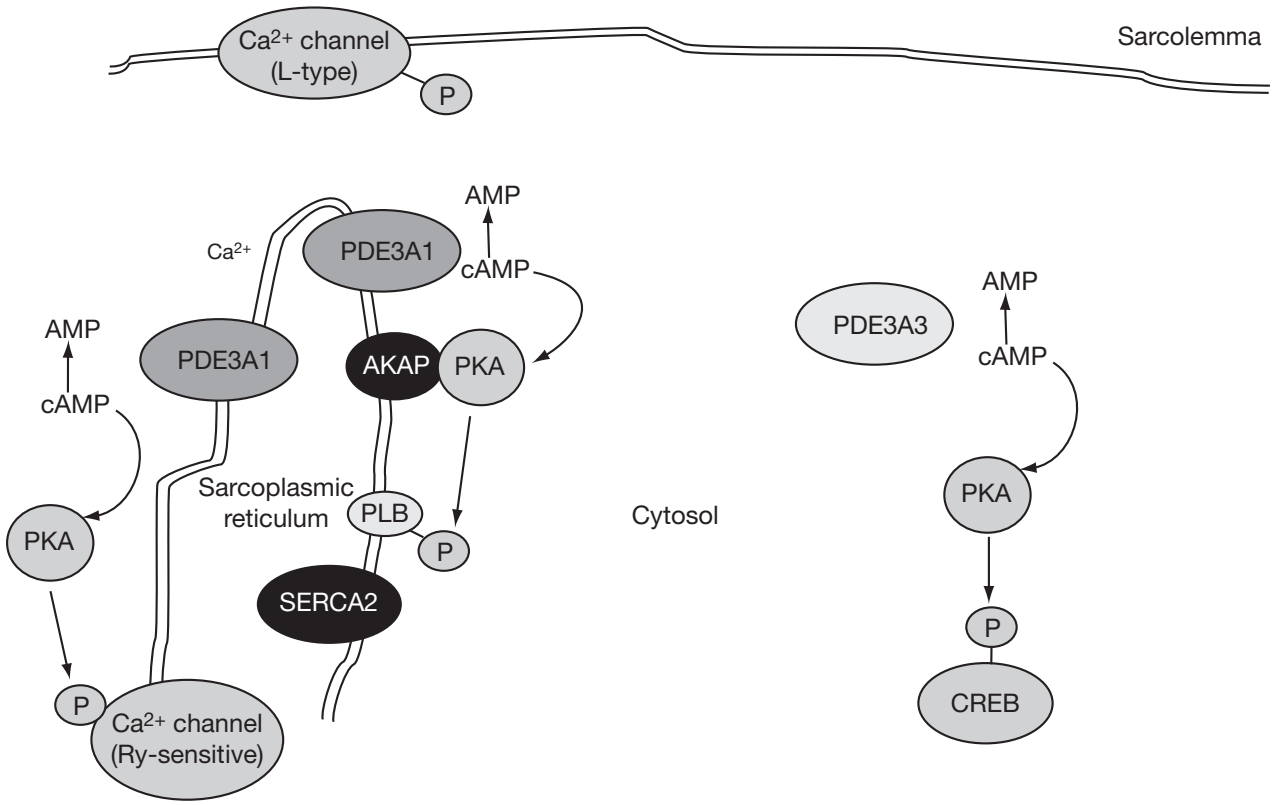

Figure 3. Individual phosphodiesterase 3 (PDE3) isoforms may regulate different responses. AKAP = A kinase anchoring protein; Ca^{2+} = calcium ion; cAMP = cyclic adenosine 3′,5′-monophosphate; CREB = cAMP response element-binding protein; P = phosphate; PLB = phospholamban; PKA = protein kinase A; Ry = ryanodine; SERCA2 = sarco-endoplasmic reticulum Ca^{2+}–ATPase. (Adapted from reference 41.)

inhibitors occurs downstream from the β_1-adrenergic receptor and therefore remains effective in the presence of β_1-blockade.[49]

Combination Therapy with Phosphodiesterase Inhibitors and β_1-Adrenergic Receptor Antagonists

With β-adrenergic receptor antagonists now widely accepted as a cornerstone of contemporary pharmacotherapy for heart failure, recent investigations have examined the effects of these agents when combined with phosphodiesterase type 3 inhibitors—a family of phosphodiesterases highly expressed in myocardial tissue.

A series of 30 patients with advanced heart failure (New York Heart Association [NYHA] functional class IV) who required intravenous inotropic agents or were assessed as too unstable to tolerate β-blockade received oral enoximone (an investigational oral phosphodiesterase 3 inhibitor) at a mean daily dose of 189 mg, followed by optimization of other heart failure pharmacotherapy including ACE inhibitors, diuretics, and digoxin.[50] Patients then received oral metoprolol with upward titration to a target dose of 100–200 mg/day. Twenty-nine patients (97%) tolerated oral enoximone therapy and 24 patients (80%) tolerated combination therapy (mean 9.4 mo). Treatment produced a 1-year survival rate of 81%, which was significantly superior to that in patients with NYHA class IV who received enalapril in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)[20] (1-yr survival 54%, p=0.01) and standard therapy in the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial[6] (1-yr survival 61%, p=0.03). It should be noted that survival rates were calculated for all 30 patients in the study—not just those receiving combination therapy. Patients also experienced significant improvements in left ventricular ejection fraction ([LVEF] baseline 0.18, final 0.28, p<0.01) and NYHA functional class (baseline 4.0, final 2.8, p<0.0001). Although the clinical utility of these intertrial comparisons may be questioned, these findings do suggest that combination therapy may improve heart failure symptoms without adverse effects on mortality (as seen in previous trials of phosphodiesterase inhibitors without concomitant β-adrenergic receptor antagonists).

In an observational follow-up study of 65 patients with advanced heart failure (NYHA class IV) who were selected for treatment with continuous intravenous milrinone (a phosphodiesterase 3 inhibitor) and β-adrenergic receptor antagonists on an outpatient basis, 14 patients (22%) were unable to tolerate β-adrenergic receptor antagonists (i.e., received milrinone monotherapy) and served as controls for the 51 patients (78%) who did tolerate combination therapy.[51] Combination therapy improved 3-year survival (69%) versus milrinone monotherapy (43%, p<0.0001), although patients unable to tolerate β-adrenergic receptor antagonists likely reflected worsened disease status at baseline. Patients receiving combination therapy also experienced no significant change in QTc interval versus baseline (from 441 to 446 msec, p=0.82), whereas patients receiving milrinone monotherapy experienced significant QTc-interval prolongation (from 436 to 469 msec, p=0.002). Inasmuch as increases in QTc intervals are associated with increased risk of high-grade arrhythmias, the reversal of QTc prolongation with combination therapy indicated that the addition of β-adrenergic receptor antagonists to milrinone may protect against milrinone-induced arrhythmias.

In a similar observational follow-up study of 16 patients with refractory heart failure (NYHA class IV) treated with continuous intravenous milrinone on an outpatient basis, 12 patients (75%) received combination therapy with β-adrenergic receptor antagonists and 4 patients (25%) who received no β-adrenergic receptor antagonists served as controls.[52] Combination therapy improved NYHA functional class in a higher percentage of patients versus placebo at 6–12 weeks (60% vs 25%) and 12–24 weeks (62% vs 50%); however, the study was not powered for statistical comparisons.

The Studies of Oral Enoximone Therapy in Advanced Heart Failure (ESSENTIAL) trial was the first randomized trial to test the addition of a phosphodiesterase inhibitor to a contemporary heart failure regimen that included the use of β-adrenergic receptor antagonists.[53] Although completed in 2004, full results of the trial have not yet been reported.[54] The ESSENTIAL trial enrolled 1854 patients with NYHA class III–IV symptoms and at least one hospitalization for worsening heart failure during the previous year. Over a mean treatment duration of 16.4 months, enoximone 25–50 mg orally 3 times/day produced a neutral mortality effect versus placebo (21.7% vs 22.6%, p=0.73). Unfortunately, this dosage of enoximone also produced no clinical benefits on heart failure measures such as

6-minute walk and patient-assessed improvement. Post hoc analyses suggested that patients with severe disease (LVEF < 0.25) and longer enoximone treatment duration may have experienced significant benefits (improved 6-minute walk test and reduced mortality), but these stratifications were not included in the primary end points. As this study remains the only randomized trial to assess combination therapy, much debate has ensued among the heart failure community. Critics of the trial note the lack of efficacy for the primary end points, whereas proponents note that the addition of enoximone to a β-adrenergic receptor antagonist–based regimen did not produce the mortality increases reported in previous trials with phosphodiesterase 3 inhibitor monotherapy. Both perspectives note that the lack of effect may be attributable to inadequate enoximone dosing (25–50 mg 3 times/day).[50] The larger question to be answered is whether phosphodiesterase inhibitors (in combination with β-adrenergic receptor antagonists) will retain this mortality-neutral effect when used at doses sufficient to produce clinical benefits. In a study already described, clinical improvement was noted at higher doses of enoximone (mean daily dose 189 mg).[50]

Compartmentation of Phosphodiesterase and Protein Kinase A Effects

With the clinical utility of combination therapy still in question, other investigators continue to focus on elucidating the mechanisms by which phosphodiesterase inhibitors affect sympathetic signaling within the myocardium.

In an anecdotal sense, the intensity of intracellular norepinephrine signaling depends on the balance of phosphodiesterase and PKA as they compete for the cAMP substrate (Figure 3[41]). Activation of PKA by cAMP increases norepinephrine effects; phosphodiesterase hydrolysis of cAMP reduces norepinephrine effects. Specific intracellular localization of PKA and phosphodiesterase may, therefore, be pivotal in determining cellular responses to norepinephrine. This theory, known as "compartmentation," suggests that regional variations in cytoplasmic concentrations of PKA and phosphodiesterase determine which PKA targets receive the most phosphorylation.[30] The efficiency of compartmented signaling may be increased by anchoring proteins that bind PKA and phosphodiesterase to specific locations within the cell.[55]

The importance of compartmentation was first documented in studies that compared the effects of β-adrenergic receptor agonists and prostaglandin E_1 on intracellular cAMP.[56–58] Both agents increased cytosolic cAMP levels, but only the β_1-adrenergic receptor agonists induced an inotropic response. The mechanism for such differing responses was attributed to the observation that β-adrenergic receptor agonists produced increases in both cytosolic and microsomal cAMP, whereas prostaglandin E_1 produced increases in only cytosolic cAMP. This suggests that changes in cAMP content have different effects depending on the intracellular compartments in which they occur.

Phosphodiesterase subtypes may have a prominent role in compartmentation effects. Phosphodiesterase 3A1 is expressed as a membrane-bound enzyme in cardiac myocytes but is absent from vascular myocytes, whereas phosphodiesterase 3A2 is both cytosolic and membrane bound in cardiac and vascular myocytes; phosphodiesterase 3A3 predominates in cytosolic fractions of cardiac and vascular myocytes.[59, 60] It was therefore proposed that phosphodiesterase 3A1 co-localizes with calcium-handling proteins on the sarcoplasmic reticulum membrane and mediates the "fine-tuning" of calcium cycling, whereas phosphodiesterase 3A3, present in the cytosol, modulates CREB regulation of gene expression.

Future Directions in Phosphodiesterase Research

With at least 11 families of phosphodiesterases identified in humans, multiple targets exist for future therapeutic intervention. For example, phosphodiesterase type 1 was recently identified in human myocardium and shows similar affinity for both cAMP and cyclic guanosine 3′,5′-monophosphate (cGMP).[61] Whereas phosphodiesterase 3 remains primarily responsible for cAMP catalytic activity in microsomal (membrane-bound) fractions, phosphodiesterase 1 is localized to Z-lines and M-lines in the sacromere and constitutes the majority of cAMP catalytic activity in soluble fractions of the myocardium. The expression of phospho-diesterase 1 in the myocardium may allow for both cAMP- and cGMP-mediated signaling to be modulated by calcium during systole. The spatially distinct activities of phosphodiesterase types 1 and 3 reinforce the significance of myocardial compartmentation and may be associated with activation

of select PKA targets. Continued research seeks to characterize the physiologic effects of phosphodiesterase 1 inhibition by using IC295 (selective phospho-diesterase 1 inhibitor) and the interplay of cGMP and cAMP on myocardial calcium signaling. [61, 62]

Conclusion

Multiple clinical trials document the benefit of β_1-adrenergic receptor antagonists in patients with heart failure. β-Adrenergic receptor antagonists nonselectively reduce PKA activity within the myocardium, masking the potential benefit of some PKA targets. In contrast with other inotropic agents, phosphodiesterase inhibitors may activate select myocardial PKA targets in the presence of continued β-blockade. Recent clinical investigations highlight the potential benefits of phosphodiesterase inhibitors combined with β-adrenergic receptor antagonists in patients with heart failure. Preliminary reports in the ESSENTIAL trial indicate the combination of phosphodiesterase inhibitor and β-adrenergic receptor antagonist to be well tolerated; however, inadequate dosing may have masked the clinical benefit and/or toxicity of enoximone.

The only phosphodiesterase 3 inhibitors approved for use in heart failure pharmacotherapy (milrinone and amrinone) exhibit selectivity for the phosphodiesterase 3 family, but no selectivity for individual phosphodiesterase 3 subtypes. Phosphodiesterase 1 inhibition shows promise in basic science research but may be years away from clinical development. Development of novel phosphodiesterase inhibitors with subtype selectivity may reveal a more meaningful role for phosphodiesterase inhibition as an addition to β-adrenergic receptor antagonist therapy in patients with heart failure.

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