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Novel approaches to targeting PDE3 in cardiovascular disease

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ABSTRACT

Inhibitors of PDE3, a family of dual-specificity cyclic nucleotide phosphodiesterases, are used clinically to increase cardiac contractility by raising intracellular cAMP content in cardiac myocytes and to reduce vascular resistance by increasing intracellular cGMP content in vascular smooth muscle myocytes. When used in the treatment of patients with heart failure, PDE3 inhibitors are effective in the acute setting but increase sudden cardiac death with long-term administration, possibly reflecting pro-apoptotic and pro-hypertrophic consequences of increased cAMP-mediated signaling in cardiac myocytes.

cAMP-mediated signaling in cardiac myocytes is highly compartmentalized, and different phosphodiesterases, by controlling cAMP content in functionally discrete intracellular microcompartments, regulate different cAMP-mediated pathways. Four variants/isoforms of PDE3 (PDE3A1, PDE3A2, PDE3A3, and PDE3B) are expressed in cardiac myocytes, and new experimental results have demonstrated that these isoforms, which are differentially localized intracellularly through unique protein–protein interactions, control different physiologic responses. While the catalytic regions of these isoforms may be too similar to allow the catalytic activity of each isoform to be selectively inhibited, targeting their unique protein–protein interactions may allow desired responses to be elicited without the adverse consequences that limit the usefulness of existing PDE3 inhibitors.

Contents

Dedication

Vincent C. Manganiello, my longtime friend and collaborator, died 10 January 2016. He was 76 years old.

Dr. Manganiello was a pioneer in the area of cyclic nucleotide phosphodiesterases. He began his work in cyclic nucleotides after coming to NIH in the late 1960s; he continued to lead the field throughout his career, and he was actively directing his research program until the very end. He and his coinvestigators cloned the cDNAs of PDE3A and PDE3B, and they carried many of the studies in which the protein–protein interactions of PDE3A and PDE3B and their roles in cardiac muscle were elucidated.

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Highly accomplished, Dr. Manganiello was the most unassuming man one could have met, unfailing warm and kind. Many of us were extraordinarily privileged to have trained under him or worked with him over the years. We remember him not only as a great scientist and colleague but also as a wonderful friend. And for many of us, those terms fail to express the full extent of our admiration, indebtedness, and affection.

This review is dedicated to his memory.

1. Introduction

Cyclic nucleotide phosphodiesterases regulate intracellular signaling by hydrolyzing cAMP and/or cGMP. Enzymes in the PDE3 family of phosphodiesterases are dual-specificity enzymes with high affinities for both cAMP and cGMP but much higher turnover rates for cAMP(Boyes & Loten, 1988; Grant & Colman, 1984). For this reason, they are thought of principally in the context of their role in regulating cAMP-mediated signaling in cardiac muscle; their cGMP-hydrolytic activity may be more important in vascular smooth muscle, as described below.

PDE3 inhibitors are used therapeutically to raise intracellular cAMP content in cardiac myocytes in patients with heart failure. In the short term, PDE3 inhibitors raise myocardial contractility, but their long-term administration leads to an increase in cardiovascular mortality (Amsallem, Kasparian, Haddour, Boissel, & Nony, 2005; Movsesian, 2015). Finding a way to target PDE3 so as to separate the mechanisms that increase contractility from those that increase cardiovascular mortality would be a significant therapeutic breakthrough. Here we review recent discoveries that present possibilities through which PDE3 may be targeted with a more favorable profile of beneficial and adverse consequences.

2. PDE3A regulates myocardial contractility

The PDE3 family of phosphodiesterases has an especially important role in regulating cAMP-mediated signaling in human myocardium (Francis, Blount, & Corbin, 2011). Two subfamilies transcribed from separate genes, PDE3A and PDE3B, have been identified (Meacci et al., 1992). Studies in knockout mice show that inotropic responses to PDE3 inhibition are preserved in *Pde3b* −/− but are abolished in *Pde3a* −/− mice, indicating that myocardial contractility is regulated by PDE3A(Beca et al., 2013). *Pde3a* ablation increases the phosphorylation of two sarcoplasmic-reticulum proteins involved in intracellular Ca^{2+} cycling(Beca et al., 2013) (Fig. 1). Phosphorylation of ryanodine-sensitive Ca^{2+} channels increases Ca^{2+} release from the sarcoplasmic reticulum during systole(Takasago, Imagawa, & Shigekawa, 1989). Phosphorylation of phospholamban (PLN) leads to its dissociation from the SERCA2 complex containing AKAP18, PKA, and PDE3A; this stimulates SERCA2 activity and increases Ca^{2+} uptake by the sarcoplasmic reticulum during diastole (Akin, Hurley, Chen, & Jones, 2013; Kranias & Hajjar, 2012). These changes in protein phosphorylation augment myocardial contractility by increasing the amplitude of intracellular Ca^{2+} transients (Beca et al., 2013).

3. PDE3 inhibitors in the treatment of heart failure

In heart failure, decreases in β-adrenergic receptor density and increases in Gαi and β-adrenergic receptor kinase activity in cardiac myocytes attenuate cAMP generation, leading to decreases in cAMP content, protein phosphorylation, and the amplitude of intracellular Ca^{2+} transients (Beuckelmann, Nabauer, & Erdmann, 1992; Bohm, Reiger, Schwinger, & Erdmann, 1994; Bristow et al., 1982; Bristow et al., 1986; Danielsen et al., 1989; Feldman et al., 1988, 1987; Neumann et al., 1988; Ungerer, Bohm, Elce, Erdmann, & Lohse, 1993; Ungerer et al., 1994). PDE3 inhibitors have been used to 'overcome' these effects by blocking cAMP hydrolysis and potentiating cAMP-mediated signaling.

In the short term, PDE3 inhibitors increase contractility in failing hearts (Anderson, 1991; Baim et al., 1983; Benotti, Grossman, Braunwald, Davolos, & Alousi, 1978; Jaski, Fifer, Wright, Braunwald, & Colucci, 1985; Maskin, Sinoway, Chadwick, Sonnenblick, & Le Jemtel, 1983; Monrad et al., 1984; Sinoway et al., 1983). With prolonged administration (e.g., months or longer), however, these benefits are outweighed by an increase in morality from sudden cardiac death, that, on meta-analysis, was ~3% per year(Amsallem et al., 2005; Cohn et al., 1998; Narahara, 1991; Packer et al., 1991, 1993; Uretsky et al., 1990). The mechanisms responsible for the increased cardiovascular mortality are likely to be separate from those that augment contractility by increasing SERCA2 activity, since overexpression of SERCA2 is *anti*-arrhythmic in animal models of ischemia/reperfusion and chronic heart failure (del Monte et al., 2004; Lyon et al., 2011). Pro-apoptotic consequences of PDE3 inhibition, though, are apt to contribute to the pathologic cardiac remodeling that occurs in this syndrome(Dorn, 2009). PDE3 inhibition in rats and *Pde3a* ablation in mice lead to

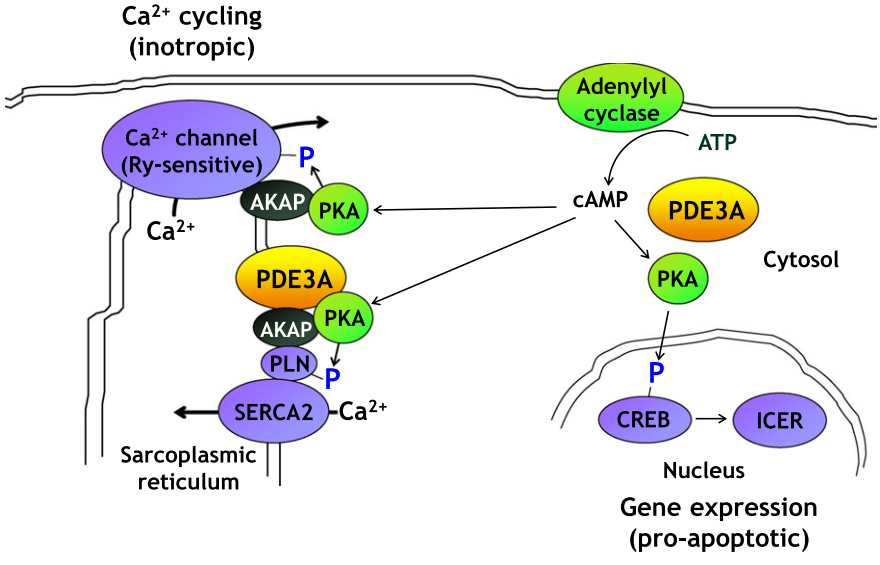

Fig. 1. Inotropic and pro-apoptotic actions of cAMP regulated by PDE3A in cardiac myocytes.