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Original article

Cardiac-directed expression of adenylyl cyclase reverses electrical remodeling in cardiomyopathy

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Abstract

Adenylyl cyclase (AC) is an effector molecule in β-adrenergic receptor signaling, catalyzing conversion of ATP to cAMP. Agents that increase intracellular levels of cAMP have been used previously to treat clinical heart failure. Recently, Roth et al. have shown that long-term cardiac-directed expression of AC_{VI}, a dominant AC isoform in mammalian cardiac myocytes, increases survival and abrogates myocardial hypertrophy in transgenic (TG) mice with $G_{\alpha q}$-associated cardiomyopathy. Indeed, it has been proposed that increasing the cardiac content of AC_{VI} is fundamentally different than other strategies used to increase cAMP function. However, one important but unexplored issue is its effects on electrical remodeling. Electrophysiological properties of $G_{\alpha q}$ mice have been characterized. Similar to other models of cardiac hypertrophy and failure, cardiac myocytes isolated from $G_{\alpha q}$ mice show prolonged action potential with reduced transient outward K^+ current (I_{to}) and inward rectifier K^+ current (I_{K1}) density compare to wild-type (WT) animals. We directly examined the electrical remodeling of cardiac-directed AC_{VI} over-expression in $G_{\alpha q}$ mice using ECG recordings and whole-cell patch-clamp recordings. Four groups of animals were used: WT (double negative), AC_{VI}, $G_{\alpha q}$ and double positive TG mice ($G_{\alpha q}/AC_{VI}$). Cardiac-directed expression of AC_{VI} results in the reversal of adverse electrical remodeling in the $G_{\alpha q}$ mice and is associated with significant improvement in the delay of cardiac repolarization and arrhythmias. Specifically, there is a normalization of I_{to}, I_{K1} and action potential duration in $G_{\alpha q}/AC_{VI}$ compared to $G_{\alpha q}$ mice. In summary, our data provide evidence that increased cardiac AC_{VI} content has a salutary effect in cardiomyopathy and cardiac electrical remodeling.

Keywords: Adenylyl cyclase; Cardiomyopathy; Electrical remodeling; K current

1. Introduction

Cardiac hypertrophy and failure are common clinical manifestations which affect an estimated 5 million Americans with mortality rate of approximately 50% in 4 years [1]. In spite of intensive investigation, the signaling mechanisms underlying the development of cardiac hypertrophy and the transition to heart failure are not completely understood [2,3].

Adenylyl cyclase (AC) is an effector molecule in β-adrenergic receptor (βAR) signaling, catalyzing conversion of ATP to cAMP [4]. Indeed, agents that increase intracellular levels of cAMP have been used previously to treat clinical heart failure [5,6], because failing hearts have been shown to have reduced amounts of cAMP [7] and impaired contractile function. However, results from clinical trials have been disappointing showing an increase in mortality with treatment using these agents. Recently, Roth et al. have made an important observation that sustained increases in cAMP level were not observed in cardiac myocytes isolated from mice over-expressing AC isoform VI (AC_{VI}) [8–11]. Furthermore, long-term cardiac-directed expression of AC_{VI} increases

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survival and abrogates myocardial hypertrophy in transgenic mice with $G_{\alpha q}$-associated cardiomyopathy [10,11]. Importantly, there were no late deleterious sequelae, as seen with over-expression of other βAR signaling elements. For example, cardiac-directed expression of β_1AR [12], β_2AR [13] and $G_{\alpha s}$ [14] was associated with initial increases in cardiac function, but with deleterious cardiac effects when examined later in life or when coexpressed in cardiomyopathic hearts. These data, taken together, support the notion that increased cardiac AC_{VI} content may have a salutary effect in cardiomyopathy. From these studies, it is reasonable to hypothesize that therapies directed towards restoring cardiac AC function, which is reduced in heart failure, may yield different results than those obtained with agents (βAR agonists or milrinone) that produce sustained elevations in intracellular cAMP levels and in turn, may have untoward cardiac effects. Indeed, manipulation of AC_{VI} may offer a potential therapeutic benefit in cardiac hypertrophy and failure.

Electrophysiological properties of $G_{\alpha q}$ mice have been characterized [15,16]. Similar to other cardiac hypertrophy and failure models, cardiac myocytes isolated from $G_{\alpha q}$ over-expression mice show prolonged action potential and reduced transient outward K^+ current (I_{to}) compared to wild-type (WT) animals, whereas Ca^{2+} current remains unchanged. Here, we hypothesize that there are salutary changes in the electrical remodeling of cardiac-directed AC_{VI} over-expression in a transgenic mouse model of $G_{\alpha q}$ over-expression induced cardiomyopathy and these changes represent one of the beneficial effects of cardiac-directed expression of AC_{VI}.

2. Methods

2.1. Transgenic mice

All animal care and procedures were approved by the University of California, Davis Institutional Animal Care and Use Committee. Animal use was in accordance with National Institutes of Health and institutional guidelines. Transgenic mice with cardiac-directed AC_{VI} expression were generated as

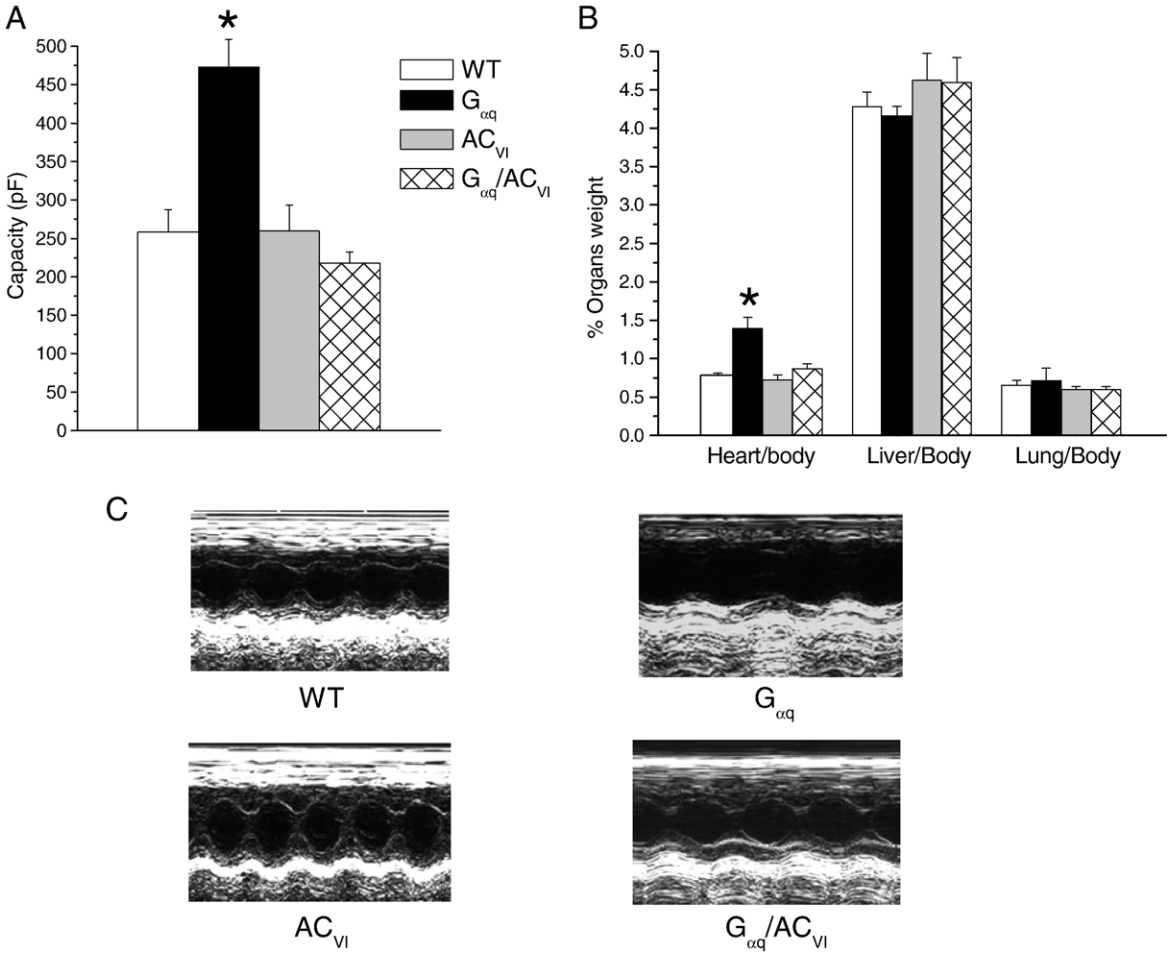

Fig. 1. Cardiac-directed expression of AC_{VI} resulted in the reversal of the cardiomyopathy in $G_{\alpha q}$ transgenic mice. (A) $G_{\alpha q}$ transgenic mice showed a significant increase in the cell capacity in single free wall LV myocytes (*$P < 0.05$ compared to WT, $n = 8$–15). Cardiac-directed expression of AC_{VI} resulted in the normalization of the cell capacity in the $G_{\alpha q}/AC_{VI}$ double transgenic mice (B, heart, liver and lung/body weight ratios in the four groups of mice. Cardiac-directed expression of AC_{VI} resulted in the normalization of the heart/body weight ratio in the $G_{\alpha q}/AC_{VI}$ transgenic mice (*$P < 0.05$ compared to WT, $n = 6$–9 animals). (C) Examples of M-mode echocardiogram obtained from the four groups of mice showing chamber dilatation and a decrease in cardiac contractility in $G_{\alpha q}$ transgenic mice. Cardiac-directed expression of AC_{VI} resulted in a significant improvement in the cardiac function in $G_{\alpha q}/AC_{VI}$ transgenic mice. Summary data are shown in Table 1.