Introduction

Contraction of the cardiac muscle is controlled by cycles of calcium release and uptake which in turn activate and deactivate access of cardiac myosin motors to calcium-activated actin-myosin myofilaments. Traditional isotropic agents used in treating acute decompensated heart failure increase cellular contractility by increasing the calcium transient. β-adrenergic agonists activate β-adrenergic receptors resulting in increased intracellular calcium and subsequent activation of the myosin ATPase in the cardiac sarcomere (Rodriguez et al., 2004). PKA activation in cardiac muscle is followed by the activation of PKM2 resulting in increased PKM activity and heart failure. β-agonists directly stimulate activity of the myosin ATPase in the cardiac sarcomere (Rodriguez et al., 2004).

Methods

In vivo experiments:

In vivo

In vivo experiments:

In vivo

In vivo

In vivo

Results

CK-1827452 increases myocyte contractility without increasing the calcium transient

To determine possible effects on the calcium transient at high concentrations of CK-1827452 experiments were conducted in the presence of the myosin inhibition BDM. BDM inhibits the myosin cross-bridges but doesn’t alter the calcium cycling. A large concentration of CK-1827452 (10 μM) overcomes BDM inhibition, but does not increase the calcium transient. In contrast, the β-adrenergic agonist isoproterenol (ISO) alters the calcium transient parameters.

CK-1827452 overcomes BDM inhibition without increasing calcium transient parameters

Individual isolated rat cardiac myocyte tracing (above) and group data (below) showing contractility and calcium transient after CK-1827452 treatment. CK-1827452 treatment elicits a significant increase in contractility with no significant change in the Fura-2 calcium ratio.

CK-1827452 lacks PDE activity

Individual myocyte tracing showing contractility and calcium transient changes after treatment alone or in combination with CK-1827452, ISO, or the PDE inhibitor milrinone. Combination treatment with CK-1827452 and ISO results in additional contractility but no additional increase in the calcium transient (no PDE inhibitory activity).

CK-1827452 increases fractional shortening

Cardiac function was determined using M-mode echocardiography.

Fractional shortening (%): Increase of cardiac function

CK-1827452 significantly increases fractional shortening.

CK-1827452 overcomes BDM inhibition

Individual isolated rat cardiac myocytes treated with CK-1827452 results in increased fractional shortening without increasing the calcium transient or inhibiting the PKA pathway.

Results (continued)

CK-1827452 increases fractional shortening in vivo...

... in Sprague Dawley rats

Echocardiography parameters after 30 min infusion of 0.25 – 1.2 mg/kg/hr CK-1827452. A dose response increase in fractional shortening (FS) is observed.

... and in animals with heart failure

Rats with myocardial infarction (MI) had similar body weights to sham controls but had increased heart wts, HW/BW ratios and decreased FS consistent with heart failure.

Abstract #1728

In Vitro and In Vivo Efficacy of the Cardiac Myosin Activator CK-1827452

RL Anderson, SH Sueoka, HM Rodríguez, KH Lee, DR Cox, R Kawsa, BP Morgan, R Sakowicz, DJ Morgans Jr, F Mallik, KA Eliahs

Cytokinetics, Inc. South San Francisco, CA

INTRODUCTION

METHODS

RESULTS

CONCLUSIONS

The cardiac myosin activator CK-1827452: • Selectively activates cardiac myosin • Increases contractility in cardiac myocytes without increasing calcium transient • Significantly increases cardiac contractility in SD rats and animals with defined heart failure • These data suggest that CK-1827452 may be a useful therapeutic in the treatment of human heart failure

REFERENCES


In vitro summary: In biochemical studies, CK-1827452 selectively activates cardiac myosin. In isolated cardiac myocytes, treatment with CK-1827452 results in increased fractional shortening without increasing the calcium transient or inhibiting the PKA pathway.

In vivo summary: In Sprague Dawley rats, CK-1827452 increases fractional shortening starting at 0.4 μM plasma concentrations, in sham and heart failure rats, infusion of CK-1827452 results in similar and significant increases in fractional shortening starting at plasma concentrations of 0.4-0.6 μM.