**INTRODUCTION**

Traditional ischemic 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 an increase in cAMP and activation of the PKA signaling cascades. Numerous proteins are phosphorylated including phospholamban that results in an increase of the calcium transient and thus contractility. Phosphorylation of PLB inhibits the calcium transient, reducing cAMP levels and resulting in an increase in the calcium transient. In addition, PKA phosphorylation also results in activation of the myocardium, thereby increasing the calcium transient. The net result is to increase myocardial contractility.

A novel approach to improving cardiac contractility is to directly activate the force-generating enzyme cardiac myosin without altering the calcium transient. We have previously reported on a class of novel molecules directly stimulating activity of the myosin ATPase in the cardiac sarcomeres (Gordon et al., 2004). In vitro experiments demonstrate that myosin activators accelerate the rate (max) transition into the strongly bound state of the α-myosin myosin enzymatic cycle reported by phosphate release (green circle - right figure above). This portion of the cycle constitutes the transition from weakly to strongly bound-state state of myosin II. By reducing the time spent in the weakly bound-state state, myosin activators increase the myosin II activity in favor of the strongly bound state, favoring myosin II activity. The objective in this study was to determine the in vitro mechanism of action of CK-1827452 and its efficacy in Spargal-Dawley rats, in rats with heart failure and in dog breeds.

**CK-1827452 is a selective cardiac myosin activator**

In bioreactor and in vitro experiments, the myosin ATPase rate is increased only in the presence of cardiac myosin demonstrating that the activity of CK-1827452 is:

1. Cardiac myosin specific
2. Not activating the regulatory apparatus

Experiments shown performed at pH 7.4 ± 0.5.

**CK-1827452 lacks PDE3 activity**

In contrast to many other agonists, CK-1827452 lacks PDE3 activity.

**METHODS**

### References


### Figures

#### Figure 1: CK-1827452 improves myocyte contractility in vitro - without increasing intracellular calcium

<table>
<thead>
<tr>
<th>CK-1827452 (µM)</th>
<th>N</th>
<th>FS (%)</th>
<th>Cell-Size (% of Baseline)</th>
<th>CV (%)</th>
<th>RF (µm)</th>
<th>% Increase</th>
<th>T90 (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>100.0 ± 3.5</td>
<td>98.9 ± 2.1</td>
<td>100.0 ± 3.5</td>
<td>100.0 ± 3.5</td>
<td>100.0 ± 3.5</td>
<td>100.0 ± 3.5</td>
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<tr>
<td>0.25</td>
<td>6</td>
<td>98.4 ± 3.5</td>
<td>97.2 ± 2.0</td>
<td>98.4 ± 3.5</td>
<td>98.4 ± 3.5</td>
<td>98.4 ± 3.5</td>
<td>98.4 ± 3.5</td>
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<tr>
<td>0.5</td>
<td>6</td>
<td>96.6 ± 4.5</td>
<td>95.1 ± 2.9</td>
<td>96.6 ± 4.5</td>
<td>96.6 ± 4.5</td>
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<tr>
<td>1</td>
<td>6</td>
<td>94.4 ± 5.5</td>
<td>93.1 ± 3.2</td>
<td>94.4 ± 5.5</td>
<td>94.4 ± 5.5</td>
<td>94.4 ± 5.5</td>
<td>94.4 ± 5.5</td>
</tr>
</tbody>
</table>

* fs = force generation

#### Figure 2: CK-1827452 increases fractional shortening in vivo - in SD rats with heart failure

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Body Weight (kg)</th>
<th>Heart Weight (g)</th>
<th>EFWR %</th>
<th>Fractional Shortening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>16</td>
<td>0.50 ± 0.042</td>
<td>1.639 ± 0.015</td>
<td>1.564 ± 0.023</td>
<td>0.361 ± 0.063</td>
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<tr>
<td>MI</td>
<td>20</td>
<td>0.34 ± 0.107</td>
<td>2.145 ± 0.107</td>
<td>2.145 ± 0.107</td>
<td>2.145 ± 0.107</td>
</tr>
</tbody>
</table>

Rats with myocardial infarction (MI) had similar body weights to sham controls, but did not have increased heart weights, HFWR ratios and decreased FS consistent with heart failure.

**Conclusions**

The cardiac myosin activator CK-1827452:

1. Selectively activates cardiac myosin
2. Increases contractility in cardiac myocytes without increasing intracellular calcium
3. Significantly increases contractility in SD rats and rats with defined heart failure and in normal dogs
4. These data suggest that CK-1827452 may be a useful therapeutic in the treatment of human heart failure.

**REFERENCES**