THE FAST SKELETAL MUSCLE TROPNIN ACTIVATOR, CK-2127107, IMPROVES MUSCLE FUNCTION IN MOUSE MODELS OF SPINAL MUSCULAR ATROPHY
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ABSTRACT

CK-2127107 is small molecule fast skeletal muscle-specific troponin activator that sensitizes the sarcomere to calcium, leading to increased muscle force in response to sub-tetanic nerve stimulation. The objective of this study was to investigate the effect of CK-2127107 on skeletal muscle function in two mouse models of spinal muscular atrophy (SMA) with varying disease severity. The 28B2-Neo and Hung Li models of SMA, corresponding to intermediate and adult-onset SMA phenotype, respectively, were evaluated in situ for plantarflexor isometric muscle force production in response to sciatric nerve stimulation. 28B2-Neo SMA mice, characterized by reduced compound muscle action potentials and motor unit number estimation, had hindlimb muscle atrophy compared to sibling controls (28B/CON).

Isometric muscle force in situ was significantly lower in 28B2-Neo SMA mice at all submaximal and tetanic rates of nerve stimulation (10 to 200Hz) compared to 28B/CON (n=11-12/group; p<0.001). In 28B/Neo SMA mice, CK-2127107 (30 mg/kg, IP) significantly increased isometric force in response to 30Hz nerve stimulation (Vehicle: 27.2 ± 2.8 mN vs. CK-2127107: 69.2 ± 2.7 mN, mean ± S.E.M, n=4-5/group; p<0.001) and resulted in a leftward shift of the force-frequency curve. The adult-onset Hung Li SMA mice also had significant muscle atrophy and a decrease in muscle force production compared to controls (ILC/CON), including reduced force at 30Hz (n=8-10; p<0.05). In the Hung Li SMA mice CK-2127107 (30 mg/kg, IP) significantly increased isometric force in response to 30Hz nerve stimulation (Vehicle: 6.8 ± 0.2 mN vs. CK-2127107: 151.1 ± 10.2 mN, mean ± S.E.M, p<0.05, n=4-5/group; p<0.001) and resulted in a leftward shift of the force-frequency curve. In summary, single doses of CK-2127107 significantly increased submaximal force in situ in two models of SMA mice. These results suggest that CK-2127107 and other fast skeletal muscle troponin activators may be viable therapeutics for improving muscle function in spinal muscular atrophy.

RESULTS

SMMA MOUSE MODEL CHARACTERISTICS

<table>
<thead>
<tr>
<th>CMAP (mV)</th>
<th>MUNE (p)</th>
<th>Body Mass (g)</th>
<th>GA Muscle Mass (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (28B/Neo) (n=12)</td>
<td>33 ± 1.3</td>
<td>349 ± 2.6</td>
<td>26.7 ± 0.7</td>
</tr>
<tr>
<td>28B2-Neo (n=12)</td>
<td>25.9 ± 0.9**</td>
<td>193.3 ± 13.8**</td>
<td>19.4 ± 0.6***</td>
</tr>
<tr>
<td>Control (Hung Li) (n=12)</td>
<td>–</td>
<td>–</td>
<td>30.9 ± 0.5</td>
</tr>
<tr>
<td>Hung Li (n=20)</td>
<td>–</td>
<td>–</td>
<td>27.4 ± 0.5***</td>
</tr>
</tbody>
</table>

Figure 1. SMA mice produced less force in situ than control mice. Control and SMA mice were subjected to active nerve stimulation at frequencies ranging from 10-200Hz. A. 28B2-Neo SMA mice produced significantly lower isometric force absolute at all stimulation frequencies. B. Hung Li SMA mice significantly lowered isometric absolute force at select sub-tetanic and tetanic stimulation frequencies. All data are expressed as mean ± SEM.

DISCLOSURES

D. Hwee, F. Malak, and E. Chinn are currently employees of Cytokinetics, Inc. and were compensated financially for their work.

C. Diodato is supported by funding from NMK Care SMA and MA.

REFERENCES


SUMMARY OF FINDINGS

- 28B2-Neo and Hung Li SMA mice exhibited significant nerve dysfunction and/or muscle atrophy and a decrease in maximum muscle force production
- Single doses of CK-2127107 increased isometric force in situ in response to sub-tetanic nerve stimulation in both SMA mouse models.
- These results suggest that CK-2127107 and other fast skeletal muscle troponin activators may be viable therapeutics for improving muscle function in spinal muscular atrophy.