NFκB Inhibitors in the treatment of Duchenne and Becker muscular dystrophy


Extra-junctional resting $\text{Ca}^{2+}$ influx is not elevated in freshly isolated adult severely dystrophic muscle fibers.

Non-dystrophic: $21.4 \pm 4.7 \times 10^{-4}$ sec$^{-1}$.

MDX: $18.15 \pm 3.2 \times 10^{-4}$ sec$^{-1}$.

Carlson et al., 2003

Passive stretch is highly damaging.

What is the mechanism?
Does in vivo inhibition of NFκB activation reduce the pathology seen in a dystrophic muscle that is subjected to chronic passive stretch?

Classified as an anti-oxidant, pyrrolidine dithiocarbamate (PDTC) has been shown to stabilize cytosolic IκB-α and reduce nuclear NFκB activation following in vivo administration in a variety of systems.


14.5 months, nondystrophic, middle TS

Non-dystrophic middle
12.5 months, mdx, caudal TS
12 months, mdx, 48 days PDTC
Caudal Middle Cephalad

Caudal

N=3

***

N=2

**

N=5

N=7

N=6

N=3

N=7

N=7

N=6
TS working diameter per unit length (μm/μm) 
[percent of nondystrophic values] 
(percent recovery)

<table>
<thead>
<tr>
<th>TS Region</th>
<th>Nondystrophic</th>
<th>MDX-Vehicle Treated</th>
<th>MDX- PDTC treated</th>
<th>4 E3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalad</td>
<td>1.21</td>
<td>0.158 [13]</td>
<td>0.350 (18)</td>
<td>0.752 (56)</td>
</tr>
<tr>
<td>Middle</td>
<td>1.673</td>
<td>0.308 [18]</td>
<td>0.366 (4)</td>
<td>0.619 (23)</td>
</tr>
<tr>
<td>Caudal</td>
<td>1.78</td>
<td>0.398 [22]</td>
<td>1.401 (73)</td>
<td>1.875 (107)</td>
</tr>
</tbody>
</table>
What is effect of chronic treatment on Percent Centronucleation?
Mature Mice: Series 2 and 3

Key:
- = Mann-Whitney Rank Sum Test P<0.05 between PDTC vs. Vehicle
* = Mann-Whitney Rank Sum Test P<0.05 between Nondystrophic

n = 139, 2
n = 201, 8
n = 365, 6
Juvenile Mice: 60 days : PDTC-treated 30 days
What is the effect of chronic PDTC treatment on resting potential in TS muscle fibers?
A1: Saline Treated

Caudal  | Middle  | Overall

N=47.5  | N=47.5  | N=94.5

A2: PDTC Treated

Caudal  | Middle  | Overall

N=30.5  | N=34.5  | N=72.5

B1: Saline Treated

Caudal  | Overall

N=46.3  | N=49.3

B2: PDTC Treated

Caudal  | Overall

N=30.2  | N=40.2

* ***

ααααα
Series 4: Saline injected

Resting Potential (mV)

Caudal: 40,5
Middle: 33,5
Overall: 73,5

Series 4: PDTC injected

Resting Potential (mV)

Caudal: 14,3
Middle: 50,3
Overall: 64,3

Nondystrophic

4Ex3
258(-20) days
13.5 months
What is the Effect of chronic PDTC treatment on Whole Body Tension?
What is the effect of PDTC treatment on fibrosis?
A  Mature MDX Costal Diaphragm

N=21
Vehicle

N=16
PDTC

B  Mature MDX Crural Diaphragm

N=20
Vehicle

N=15
PDTC
Sulfasalazine

- Blocks NFκB pathway by inhibiting IKK (Weber et al., Gastroenterology, 119, 1209-1218, 2000).

- Effective in human skeletal muscle explants obtained from pregnant women (Lappas et al., Endocrinology, 146 (3), 1491-1497, 2005).

- Currently used in the treatment of inflammatory disorders such as ulcerative colitis and juvenile rheumatoid arthritis.
Electrophoretic shift assay – mdx costal diaphragm

Vehicle  SS
Daily sulfasalazine treatment (68 days) improves resting membrane potential in mdx TS
Daily treatment with sulfasalazine (60 to 90 days) improves tension development in the isolated mdx gastrocnemius muscle.
Summary

- Daily treatment with PDTC improves morphology of mdx TS muscle, improves resting potential, moderately improves whole body tension, produces slight increases in gastrocnemius tension, and has no effect on fibrosis.

- Daily treatment with sulfasalazine improves resting potential in TS and tension development in mdx gastrocnemius preparation (preliminary).

- Clinical trials?
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