**THE FAST SKELETAL TROPONIN ACTIVATOR, CK-2017357, IMPROVES RESISTANCE TO FATIGUE IN HEALTHY, CONSCIOUS RATS**

Adam R. Kennedy, Nathan Heald, Arash Pakdel, Julie Ryans, Alan Russell, Tim Much, David Poole, Sue Hageman, Steve Copp, Fady I. Malik, Jeffrey R. Jasper

Preclinical Research, Cytokinetics Inc, South San Francisco, CA, ‘Department of Anatomy & Physiology, Kansas State University, Manhattan, KS

**ABSTRACT**

Fast skeletal muscle fatigue is characterized, as when O2 delivery fails to keep pace with energy production, by a reduced rate of force generation, a reduced rate of force decay, and a reduced ability to undergo repeat contractions. This study evaluated the effects of CK-2017357, a novel activator of fast skeletal troponin complex that increases troponin calcium affinity and sensitizes the sarcomere to calcium, on resistance to fatigue in healthy, conscious rats. Rats administered CK-2017357 showed a dose-dependent increase in running time on a slowly accelerating rotarod, with 3 mg/kg dose showing more than a doubling of running time at maximum dose tested (Fig 3A). Rats administered compounds previously shown to improve performance in other exercise assays showed no significant effect. Control treatments were shown based on those associated with the amelioration of central (Caffeine, Dasab) and muscular (Creatine, Boidine) fatigue as well as phosphoserine, which has been suggested to function in a dual manner (Farrell, 1976). (Fig 3B).

**RESULTS: TREADMILL**

Doses of 10 and 20 mg/kg of CK-2017357 resulted in an increase in treadmill running time of 20% over baseline and 50% over vehicle control (Fig 2A). Equivalent increases were seen in distance run (Fig 2B).

**RESULTS: ROTAROD**

Rats administered CK-2017357 showed a dose-dependent increase in running time on a slowly accelerating rotarod, with 3 mg/kg dose showing more than a doubling of running time at maximum dose tested (Fig 3A).

**INTRODUCTION**

Muscle fatigue is a result of a combination of factors including reduced blood flow, accumulation of metabolites, and contraction-induced muscle damage. Studies of contractile function in fatigue have used a variety of protocols, including static contractions and concentric and eccentric exercises. However, these results reflect reduced performance under laboratory conditions. Endurance-trained rats, for example, demonstrate increased contractile performance under conditions that reduce muscle performance, suggesting that these results reflect reduced contractile performance under laboratory conditions. Endurance-trained rats, for example, demonstrate increased contractile performance under conditions that reduce muscular performance. In our fatigue assays, rats showed a sustained increase in rotarod time to fall when administered CK-2017357, a molecule of the fast troponin complex, that retains increased contractile performance and sensitizes the sarcomere to calcium. This suggests that CK-2017357 increases contractile performance in both healthy and endurance-trained animals.

**METHODS**

General Health: In the study, 10 rats were maintained in accordance with the Guide of the Care and Use of Laboratory Animals of the Institute. The Federal Animal Welfare Act and the Health Care and Education Amendment to the Animal Welfare Act apply.

Treadmill Running Protocol

- CK-2017357 or Vehicle dosed 30 min prior to test.
- Animals acclimated to walking on a treadmill for 5 min before resting.
- A second training session of an increasing speed (constant speed (10 RPM). The rats were acclimated to walk on the drum for 5 minutes before resting.

Rotarod Running Protocol

- CK-2017357 or Vehicle dosed 30 min prior to test.
- Animals acclimated to walking on a rotarod for 5 min before resting.

**RESULTS**

**TREADMILL**

**Results for Treadmill Test**

- Doses of 10 and 20 mg/kg of CK-2017357 resulted in an increase in treadmill running time of 20% over baseline and 50% over vehicle control.
- Equivalent increases were seen in distance run.

**ROTAROD**

**Results for Rotarod Test**

- Rats administered CK-2017357 showed a dose-dependent increase in running time on a slowly accelerating rotarod, with 3 mg/kg dose showing more than a doubling of running time at maximum dose tested.

**DISCUSSION**

The fast skeletal muscle troponin activator, CK-2017357, improves resistance to fatigue in healthy, conscious rats. The results suggest that CK-2017357 increases contractile performance in both healthy and endurance-trained animals, and provide a potential therapeutic approach for treating sarcopenia.

**REFERENCES**