

Treatment with RRx-001, a Minimally Toxic NLRP3 Inhibitor in Phase 3 Clinical Trials, Improves Exercise and Skeletal Muscle Oxidative Capacity in Untrained Mice

Authors : Pedro Cabrales, Scott Caroen, Tony R. Reid, Bryan Oronsky

Abstract : Introduction and Purpose RRx-001 is an NLRP3 inhibitor and Nrf2 agonist in Phase 3 trials for the treatment of cancer. The purpose of this study was to examine whether treatment with RRx-001, given its anti-inflammatory and antioxidant properties, improved exercise and skeletal muscle oxidative capacity in mice on the general premiss that better health outcomes correlate with more activity. Material and Methods Male and female adult mice (n=6 per group) were subjected to an endurance exercise capacity (EEC) test until exhaustion on a motorized treadmill after 3 once weekly doses of either RRx-001 5 mg/kg, RRx-001 2 mg/kg, or vehicle. The EEC protocol consisted of a treadmill velocity of 30 meters per min at an uphill inclination (slope of 10%) until the mice reached fatigue, which was defined as the inability of the mice to maintain the appropriate pace despite continuous hand stimulation for 1 min. The concentration of malondialdehyde (MDA), an indicator of lipid peroxidation, and creatine kinase (CK), an indicator of muscle damage, in the blood samples collected immediately after the acute exercise was determined with a commercial ELISA assay kit. Results The exhaustive exercise times of the RRx-001 groups were significantly longer than that of the vehicle group (p<0.05) by weeks 2 and 3. In addition, MDA levels in the gastrocnemius, soleus, and extensor digitorum longus muscles were significantly lower than those of the vehicle group were (p<0.05), as were the serum CK levels (p<0.05). Conclusions In conclusion, this study found that RRx-001 has anti-fatigue properties, as evidenced by an increase in exercise capacity with RRx-001 treatment, and protects against strenuous exercise-induced muscle damage and lipid peroxidation. This data potentially supports the use of RRx-001 in the clinic to improve exercise performance and reduce physical fatigue.

Keywords : RRx-001, anti-fatigue, muscle protection, increased exercise tolerance, lipid peroxidation

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