

## **Treatment with EUK-134 Enhance Anabolic Akt/mTOR/p70S6kinase Pathways, Protecting Against Muscle Atrophy in the Rat Soleus in a 7 Day Hindlimb Unloading**

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### ABSTRACT

Muscle atrophy occurs with mechanical unloading, disease and aging. Mechanical unloading occurs with bedrest, microgravity, and casting/immobilization, all of which elicit the unloading-induced phenotype: (a) reduction of muscle fiber cross-section area (CSA) and (b) a shift from slow-twitch to fast-twitch muscle fibers. Unloading-induced muscle fiber atrophy appears to be a consequence of both decrease in contractile protein synthesis combined with increased protein catabolism. Oxidative stress has been cited as potential contributing factor to the unloading phenotype, although the mechanisms remain unresolved and controversial. We recently reported that a superoxide dismutase/catalase mimetic (EUK-134) reduced muscle atrophy, fiber-type shift, and pro-catabolic signaling. The purpose of this study was to test the hypothesis that EUK-134 would attenuate loss in a canonical, pro-anabolic signaling pathway involving phosphorylation of Akt, mTOR, and p70S6K and would ameliorate muscle fiber atrophy after seven-days hindlimb unloading. Male Fisher-344 rats were divided into three groups: ambulatory control group (CON, N=11), 7 days of hindlimb unloading plus saline injections (HU, n=11), or 7 days of hindlimb unloading plus 3 mg/kg/day EUK-134 (HU-EUK, n=9). The soleus muscles from both hindlimbs were dissected for histochemistry and immunofluorescence analyses. The soleus muscle of the HU group exhibited a decrease in CSA compared to the CON group, while soleus muscle fiber CSA from HU-EUK group was greater than the HU group, but lower than CON. Furthermore, the HU group displayed a partial shift from slow-twitch to fast-twitch, an effect attenuated by EUK-134. The ratio of phosphorylated Akt to total Akt was significantly lower in the HU group compared to the CON group. However, the p-Akt/Akt was significantly higher in the HU-EUK group vs. HU group, but lower than the CON. The ratio of phosphorylated m-TOR to total m-TOR from the HU group was not different than controls. However, the ratio of p-mTOR/mTOR was a significantly higher in the EUK group compared to the CON group. Moreover, the HU group displayed a decrease in phosphorylation of p70S6Kinase, while but treatment with EUK-134 enhanced phosphorylation of p70S6Kinase. Therefore, our data are consistent with the hypothesis that EUK-134 protects anabolic signaling in the unloaded rat soleus.