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Influence of HDAC1 inhibitor on the E3-ligases expression in rat soleus during hindlimb unloading

Svetlana Belova[1,2],Ekaterina Mochalova[2],Boris Shenkman[2],Tatiana Nemirovskaya[1,2]
1.Lomonosov Moscow State University
2.Institute of biomedical problems of the Russian Academy of Sciences

Objective Muscle unloading leads to its atrophy development. The MuRF-1 and MAFbx E3-ligases expression is increasing under this condition. FOXO3 was considered to be the only transcription factor that triggers E3-ligases expression. Beharry A.W. et al pinpoints HDAC1 as a primary regulator of FoxO in skeletal muscle that is both sufficient and required for skeletal muscle atrophy. We aimed to determine the role of histone deacetylase 1 (HDAC1) proteins in activation of MuRF-1 and MAFbx E3-ligases expression at the early stage of muscle unloading.
Methods We investigate it by CI-994 (inhibitor of HDAC1) administration in male Wistar rats (180-200 g) upon 3-day hindlimb suspension. The method of hindlimb suspension was described in Morey-Holton E & Globus R (2002). 24 animals were divided into 3 groups (n=8 in each): C-control, CI - hindlimb suspension with CI-994 (i.p. 1 mg/kg/day), or placebo (HS group) administration. The animals were anaesthetized with an i.p. injection of tribromoethanol (240 mg/kg), soleus muscles were surgically excised, frozen in liquid nitrogen. The Western blot and RT-PCR analyzes were done. The statistical analysis was performed using REST 2009 v.2.0.12 and Bio-Rad CFX Manager programs at the significance level set at 0.05. The significant differences between groups were statistically analyzed using Mann-Whitney test.
Results The evaluation of the levels of mRNA expression of MuRF-1 and MAFbx showed that CI-994 treatment inhibited unloading induced up-regulation of MAFbx in CI group but had no effect on mRNA expression of MuRF-1. After unloading, mRNA expression of MAFbx increased 2.12-fold ($p < 0.05$) in HS group. There were statistically significant differences in MAFbx mRNA expression between HS and CI groups. When compared with the control, unloading increased MuRF-1 mRNA expression 1.67- and 1.56-fold in HS and CI groups, respectively. CI-994 treatment also inhibited unloading-induced upregulation of mRNA expression of ubiquitin. The levels of ubiquitin mRNA expression when compared with the control were 4.21- and 2.32-fold in HS and CI groups, respectively. We did not find any differences in the content of phosphorylated anabolic signaling system components (Akt/mTOR/S6k) between both suspended groups (CI and HS).
Conclusions Therefore, HDAC1 inhibiting prevented hindlimb suspension-induced up-regulation of MAFbx and ubiquitin, but did not any effect MuRF-1expression.
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