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p38 MAPK controls of E3-ligases expression and soleus atrophy attenuation in rat upon hindlimb unloading.

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Objective Unloading causes rapid skeletal muscle atrophy mainly due to the increased protein degradation. Muscle proteolysis results from the activation of ubiquitin-proteasome systems. The ubiquitination proteins are carried out by muscle-specific E3 ubiquitin ligases – MuRF-1 and MAFbx. It is known that MuRF-1 and MAFbx expression significantly increases on the third day of muscle unloading. We tested the hypothesis that p38 MAPK participates in the regulation of E3 ligases expression and the development of skeletal muscle atrophy during unloading. To check this idea we inhibited p38 MAPK by VX-745.
Methods 21 male Wistar rats were divided into 3 groups (7 rats in each group): intact control (C), rats suspended for 3 days (HS) and rats suspended and injected i.p. with VX-745 (10 mg/kg/day) (VX). The hindlimb suspension was carried out according to Morey-Holton technique. The animals were anaesthetised with an i.p. injection of tribromoethanol (240 mg/kg). Under anesthesia, the m.soleus were excised, frozen in liquid nitrogen, and stored at -80°C until further analysis. All procedures with the animals were approved by the Biomedicine Ethics Committee of the Institute of Biomedical Problems of the Russian Academy of Sciences/Physiology section of the Russian Bioethics Committee. The statistical analysis was performed using the REST 2009 v.2.0.12 and Origin Pro programs at the significance level set at 0,05. The results are given as median in percent and interquartile range (0.25-0.75).
Results The muscle weight in HS group was significantly reduced (72,3±2,5 mg) compared to C (83,0±3 mg), $p<0.05$, while the soleus weight of VX group didn't differ from the control (84.2±5 mg). The MuRF1 mRNA expression was elevated dramatically in HS group (165 (138-210) %) when compared with the control (100 (64.6-112.5) %), $p<0.05$. In the VX group the level of MuRF1 mRNA expression (127 (105-138) %) didn't differ from the control group. The MAFbx mRNA expression was observed to increase equally in both suspended groups (294 (265-342) % and (271 (239-309) %).) vs C (100 (91-106) %) so, VX-745 administration did not have any significant effect on its expression. We also found that the level of ubiquitin mRNA expression in the soleus of HS rats was higher (423 (325-485) %) in comparison with the C group (100 (78-166) %, $p<0.05$) while VX-745 injection prevented increasing the mRNA ubiquitin expression (200 (190-237) %). We discovered that the elevation of calpain-1 mRNA expression upon HS was prevented by VX-745 administration and its level didn't differ from the control group (C - 100 (97-105) %, HS – 120 (116-133) %, VX - 107 (100-115) %, $p<0.05$).
Conclusions Thus, the results indicate that the p38 MAPK signaling pathway takes part in the regulation of E3-ligase MuRF1 but not MAFbx expression. The p38 MAPK inhibition prevents muscle atrophy and the elevation of ubiquitin and calpain mRNA expression at the early stage of hindlimb unloading. This work was supported by RFBR grant No.17-04-01838.