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The shifted balance of high-energy phosphates drives the AMPK dephosphorylation and reduced slow myosin expression during unloading

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Objective Mechanical unloading of postural muscles results in both muscle atrophy and a slow to fast fibre type transition. The cause of such changes is a reduction in slow-type MyHC isoform expression and an increase in fast-type MyHC isoform expression. It is believed that calcineurin/NFAT signalling pathway and AMP-activated protein kinase (AMPK) are involved in the regulation of slow-type MyHC isoform. Previously we showed that AMPK phosphorylation is significantly decreased in rat soleus at the early stage of mechanical unloading. We found, that stimulation of AMPK activity at the early stage of gravitational unloading prevents a decline of slow MyHC expression. We assumed that a decrease in AMPK activity in rat soleus at the early stage of gravitational unloading could be associated with changes in the ratio of intracellular high-energy phosphates (ATP/ADP). The aim of the study was to investigate the impact of high-energy phosphates ratio changes on AMPK activity and slow-type MyHC isoform expression in rat soleus muscle at the early stages of gravitational unloading.
Methods To verify the hypothesis, we used administration of β-guanidinopropionic acid (βGPA), before (6 day) and during 24-h hindlimb suspension. The content of phospho-AMPK, phospho-ACC, phospho-PKD, HDAC4/5 in rat soleus was determined by Western-blotting. The amount of MyHCI(β) pre-mRNA and mRNA was evaluated by RT-PCR.
Results After 24-h HS we observed a decrease ($p<0.05$) in phospho-AMPK content *vs*. control group, but in HS+ βGPA group didn't differ from the control. After 24-h unloading we found a significant increase in the content of nuclear HDAC4 in the HS group, but in the HS+ βGPA group the content of nuclear HDAC4 didn't differ from the control group. 24-h unloading resulted in a decrease in MyHCI(β) pre-mRNA and mRNA expression *vs.* the control group. The expression level of MyHCI(β) pre-mRNA and mRNA in HS+ βGPA group didn't differ from the control.
Conclusions Thus βGPA administration prevents a decline in AMPK phosphorylation. Therefore, we can conclude that at the early stage of gravitational unloading an accumulation of high-energy phosphates (ATP, ADP and creatine phosphate) takes place and leads to reduced AMPK activity and a slow to fast myosin fibre type transition. The study was supported by Russian Science Foundation grant # 18-15-00107.