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Effects of dynamic foot stimulation on GSK-3 beta signaling pathway in rat soleus muscle under hindlimb unloading

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Objective It is known that under simulated microgravity GSK-3 beta phosphorylation (Ser 9) is decreased [Mirzoev et al., 2016] which is associated with the activation of its kinase activity. GSK-3 beta activation may lead to NFATc1 export from myonuclei resulting in a slow-to-fast myosin shift in soleus muscle and may cause a decrease in muscle oxidative capacity and protein synthesis [Glass, 2003, Theeuwes et al, 2017].

It was demonstrated that GSK-3 beta Ser 9 phosphorylation is decreased in response to nitric oxide synthase inhibition [Martins et al., 2011]. Under unloading conditions, the content of NO as well as nitric oxide synthase is attenuated in rat soleus muscle [Tidball et al., 1998; Lomonosova et al, 2011]. Dynamic foot stimulation (DFS) of the soles of the feet results in an increase of neuromuscular activation [Muller et al., 2005] of the lower limb muscles and prevents nitric synthase content decrease during 7-day exposure to dry immersion [Moukhina et al, 2004; Shenkman et al., 2004]. The aim of our study was to analyze the effect of rat dynamic foot stimulation during early unloading on GSK-3 beta phosphorylation and some of its downstream targets.

Methods Male Wistar rats were randomly assigned to vivarium control, 1-day unloading and 1-day unloading with DFS. The pressure stimulation protocol mimicked the normal animal walking (104 mm Hg pressure, 4 Hz frequency and 250 ms signal duration) for a total of 20 min followed by a 10-min rest interval for 4 hours.

Results We found that 1-day unloading caused a significant decrease ($p < 0.025$) in NFATc1 nuclear content as well as slow myosin (MHC I (beta) isoform) mRNA expression. In the 1-day unloading group, the level of glycogen synthase 1 phosphorylation (Ser 641), which is a direct GSK-3 beta target, was significantly higher than that in the control group, although a decrease in GSK-3 beta Ser 9 phosphorylation in the 1-day unloaded group was not statistically significant compared to the control group. However, in the DFS-treated unloaded rats the level of GSK-3 beta phosphorylation was significantly higher than in the untreated unloaded rats. NFATc1 nuclear content, slow myosin mRNA expression and glycogen synthase 1 phosphorylation (Ser 641) did not differ from the control group. The glycogen content in soleus muscles of both unloaded groups was higher than in the control group, which is in accordance with previous studies [Henriksen and Tischler, 1988], but in DFS subjected unloaded group the glycogen content was higher compared to the untreated unloaded group.

Conclusions Thus, we found that dynamic foot stimulation during 1-day hindlimb unloading leads to GSK-3 beta inactivation and prevention of both NFATc1 myonuclei export and the decrease in MyHC I beta expression.

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