The role of glycogen synthase kinase-3 beta in the regulation of ribosome biogenesis in rat soleus muscle under hindlimb unloading

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It is well-established that mechanical unloading results in a significant reduction in the rate of muscle protein synthesis and subsequent fiber atrophy and loss of muscle mass. To date, new therapies are needed to tackle the problem associated with disuse-induced skeletal muscle atrophy. However, molecular mechanisms involved in the regulation of translational capacity under disuse conditions are poorly explored. Glycogen synthase kinase-3 beta (GSK-3beta), which is known to negatively regulate protein synthesis (PS), is activated in rat soleus muscle under unloading conditions. We hypothesized that inhibition of GSK-3beta activity during hindlimb unloading (HU) would reduce unloading-induced downregulation of ribosome biogenesis in rat soleus muscle. Wistar rats were randomly divided into 3 groups: 1) vivarium control (C), 2) 7-day HU, 3) 7-day HU + daily injections (4 mg/kg) of AR-A014418 (GSK-3beta inhibitor). GSK-3beta and glycogen synthase 1 (GS1) phosphorylation was measured by Western-blotting. The key markers of ribosome biogenesis were assessed via agarose gel-electrophoresis and RT-PCR. As expected, 7-day HU resulted in a significant decrease in the inhibitory Ser9 GSK-3beta phosphorylation and an increase in GS1 (Ser641) phosphorylation compared to the C group. Treatment of rats with GSK-3beta inhibitor prevented HU-induced increase in GS1 (Ser641) phosphorylation which was indicative of GSK-3beta inhibition. Administration of GSK-3beta inhibitor also prevented unloading-induced downregulation of c-Myc expression as well as decreases in the levels of 45S pre-rRNA and 18S+28S rRNAs. These AR-A014418-induced alterations in the markers of ribosome biogenesis were paralleled with partial prevention of a decrease in the rate of PS. Thus, inhibition of GSK-3beta during 7-day HU is able to attenuate a decrease in translational capacity and the rate of PS in rat soleus muscle. The study was supported by the Russian Science Foundation grant No. 17-75-20152.