INFLUENCE OF AN ACID SPHINGOMYELINASE INHIBITOR ON ADVANCED GLYCATION END PRODUCTS IN THE RAT SOLEUS MUSCLE UNDER 14-DAY FUNCTIONAL UNLOADING

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Introduction. Prolonged bed rest, limb immobilization, and exposure to microgravity during space flight can lead to atrophic changes in postural skeletal muscles. It has been shown that one of the key mechanisms underlying these changes is an increase in muscle ceramide (Cer) levels due to the activation of sphingomyelinase-mediated hydrolysis of sphingomyelin. In particular, the inhibition of acid sphingomyelinase (ASM) enables to lower Cer levels and mitigate muscle atrophy (Bryndina I.G. et al., 2021; Protopopov V.A. et al., 2024). It has also been shown that the signaling pathway of advanced glycation end products (AGEs) realized through their RAGE receptor is upregulated in hindlimb muscles after 7 days of unloading (T. Egawa et al., 2021). However, it is unclear whether there is a direct relationship between changes in the sphingolipid pathway (ASM/Cer) and the AGE/RAGE signaling pathways.

Aim of the study. To investigate the effect of ASM inhibitor on the levels of Cer, RAGE and AGEs in rat soleus muscle under 14-day functional unloading.

Materials and methods. Experiments were conducted on male white rats weighing 200-250 g. Functional unloading of skeletal muscles was modeled according to the Ilyina-Novikov method, modified by Morey-Holton (hindlimb suspension, HS). The rats (n=18) were divided into three groups: (1) intact control, (2) HS for 14 days, (3) HS for 14 days with administration of ASM inhibitor amitriptyline.

To determine the influence of the AGE signaling pathway on ASM activation and Cer levels in the soleus muscle, an *ex vivo* experiment was performed on male white rats (n=4). In this experiment, one soleus muscle of each rat was incubated in physiological saline (Krebs solution) with AGEs, while the contralateral muscle was incubated without AGEs and served as a control. After the end of HS, muscles were removed under general anesthesia.

In the *in vivo* experiment, Cer, ASM, RAGE, AGEs and reactive oxygen species (ROS) levels were assessed in muscle cross sections by fluorescence microscopy using appropriate antibodies and reagents. Western blot analysis was performed to determine RAGE levels, with GAPDH as a loading control. In the *ex vivo* experiment, Cer and ASM levels were also detected by fluorescence microscopy. Image analysis was performed using NIS-elements D and ImageJ software. Statistical analysis was carried out with Statistica 6.0 and RStudio using the Kruskal-Wallis and Mann-Whitney tests. Differences were considered statistically significant at $p<0.05$.

Results and discussion. Fourteen-day functional unloading led to an increase in Cer, ASM, ROS, AGEs and RAGE, as confirmed by fluorescence microscopy data. Western blot analysis revealed a significant increase in RAGE compared to the control group. The inhibition of ASM decreased ASM and Cer levels, but had no effect on AGEs or RAGE in comparison with the untreated group. No changes in RAGE were observed by WB under these conditions. In the *ex vivo* experiments, exogenous AGEs added to soleus muscle samples, did not induce detectable changes in Cer or ASM muscle levels.

Conclusion. Thus, 14-day unloading leads to ASM/Cer upregulation and increase in AGE and RAGE levels in the soleus muscle. ASM inhibitor amitriptylin does not affect RAGE and AGEs, indicating the absence of the direct interaction between ASM/Cer and AGEs/RAGE pathway in muscles.

CARDIOVASCULAR RESPONSE TO PHYSICAL ACTIVITY AND ADDITIONAL WEIGHT LOAD IN MALE AND FEMALE STUDENTS

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Introduction. There are various functional load tests to study the state of the cardiovascular system, which allow identifying the latent stage of cardiovascular pathology, as well as assessing the reactivity of the cardiovascular system. This is relevant, since it allows assessing the functional reserve of the body, as well as identifying cardiovascular pathology in its compensated stage.

Aim of the study. The aim of the study was to conduct a new load test, which included, in addition to physical activity, an additional weight load.

Materials and methods. The studies were conducted on 29 students of both sexes (18 girls and 11 boys) aged 18-25 years. The studies included students climbing two flights of stairs with a total of 28 steps. The initial arterial systolic and diastolic pressure, as well as systolic and diastolic pressure and their changes following physical activity after students climbed and after students climbed the stairs with a 10 kg load were determined. The changes in pulse pressure and heart rate were also determined. The obtained data were processed using nonparametric statistics methods, the data were expressed as a median and the lower and upper quartiles. The data was considered reliable at $p<0.05$.

Results and discussion. As a result of the studies, the initial systolic pressure in girls was 115.5 [102; 122] mm Hg, diastolic pressure was 76.0 [70; 80] mm Hg. In young men, the initial systolic pressure was 129.0 [116; 136] mm Hg, $p<0,05$, diastolic pressure was 75.0 [69; 83] mm Hg. The initial pulse pressure in girls was 45.5 [35; 50] mm Hg, in young men – 53 (41; 62) mm Hg, $p<0,05$. The initial heart rate in girls was 82 [73; 90] beats per minute, in young men it was 81 [65; 91] beats per minute. After performing the load by climbing