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Exercise and High-Fat Diets Upregulate Endoplasmic Reticulum Membrane Protein Sensors and Muc2 in Female Mice

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A dense dual layered mucus barrier, comprised of the muc2 mucin glycoprotein, protects the colon epithelium from luminal microbes and the external environment. The complexity and high secretory output of muc2 makes it prone to misfolding which activates the unfolded protein response (UPR) contributing to endoplasmic reticulum (ER) stress if unresolved. Interestingly, high fat diets have shown to induce colonic epithelial stress and inflammation which may be attenuated by exercise. **PURPOSE:** We aimed to examine impact of a high-fat diet (HFD) and exercise on the gene expression of factors involved in the UPR and ER stress in male and female mice colon. **METHODS:** 56 (n=7/group) 6-week old C57BL/6NTac male and female mice were weighed and randomly assigned to one of 4 groups: (1) control-diet sedentary (CDS, 10% fat diet, Research Diets); (2) very high-fat diet sedentary (VHFS, 60% fat, Research Diets); (3) control-diet exercise (CDX); and (4) very high-fat diet exercise (VHFX) for 12 weeks. Mice had *ad libitum* access to food and water. Exercised mice had free access to a running wheel in their cages. Food intake was monitored every other day and body weights once per week. After 12 weeks animals were sacrificed. Total RNA was extracted from colon tissue fixed in RNA*later* and converted into cDNA using the RNeasy Mini and First Strand kits. qRT-PCR was performed using a custom RT2-profiler PCR array (Qiagen). Ct values were normalized to GAPDH and unpaired student t tests were used to analyze group means of ΔCt values for each sex. A difference of mean with a p value of $\leq$ 0.05 was considered statistically significant. Relative expression to CDS groups was assessed using the ΔΔCt method. **RESULTS:** For females, Atf6 and Ire1β expression was increased in VHFX mice (0.9 and 1.1-fold times) compared to VHFS (0.6-fold times; p = 0.001 and p = .008). Muc2 expression was significantly increased in CDX mice (2.3-fold times) compared to VHFS (0.7-fold times; p = 0.02). In males, no significant differences in the expression of any factor was observed. **CONCLUSION:** High-fat diets coupled with exercise increase the expression of endoplasmic reticulum membrane protein sensors involved in the unfolded protein response in females. Exercise increases muc2 expression in females.