Can exercise protect against chronic stress induced cerebral microvessel changes in Lean and Obese Zucker rats?

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Background: Chronic stress-induced depression is a major cardiovascular risk factor, and metabolic Syndrome (MetS) is linked with depression. The relationship among chronic stress/depression (UCMS), MetS, CVD, and cerebrovascular dysfunction is poorly understood. We determined how UCMS and Exercise training affected cerebral microvessels density (MVD), and the pro (nitric oxide, VEGF, STAT3) and anti (TSP-1) angiogenic factors. We hypothesize that UCMS will decrease MVD in Obese Zucker Rats (OZR = MetS), and exercise training will prevent this rarefaction by increasing pro-angiogenic mediators, while reducing anti-angiogenic factors including oxidative stress.

Methods: Nine-week old lean rats (LZR) and OZR were randomly assigned (n=6/group) to: Control(C), Exercise (EX), subjected daily to an UCMS, and EX+UCMS for 8 weeks. At 17 weeks, brains were removed and snap frozen in Tissue Tek medium. Cortex MVD were measured by fluorescence IHC (rat anti-CD31 antibody). Oxidative stress was assessed in cerebral tissue by ELISA technique (anti 3-Nitrotyrosine antibody) and by DHE. Cerebral inflammatory and angiogenic markers for STAT3, VEGF and TSP-1 were measured by western blot or ELISA.

Results: MVD was decreased (-31%, $p<0.05$) in the cortex from OZR-UCMS vs. OZR control. Exercise training attenuated UCMS induced decreased MVD in OZR by 41%. In contrast, there were no significant differences (8% decrease to 4% increase) in MVD among LZR groups. In both LZR and OZR UCMS increased oxidative stress, and decreased nitric oxide in the cerebral vessels. Although VEGF results were not yet significant, a slight decrease was seen in OZR UCMS that was recovered with exercise training in UCMS. Initial data also suggests that TSP-1, which is higher in OZR vs. LZR control, is also influenced by UCMS, and Ex. Compared to LZR-C, LZR-UCMS had an 74% increase in STAT3. Although both OZR-C and OZR UCMS exhibited significantly increased STAT3 phosphorylation compared to LZR-C, there was no difference between OZR-C and OZR UCMS. Both LZR-Ex and OZR-Ex attenuated UCMS induced elevated STAT3 activity.

Conclusion: Taken together, UCMS drives the development of decreased brain MVD in OZR. Chronic stress and obesity both independently increased STAT3 signaling in the brain, which was then abrogated by exercise in both lean and obese animals. Exercise also prevented the onset of cortical rarefaction seen in OZR-UCMS. We are further exploring TSP1 and VGEF pathways.

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