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NFκB Inhibition Negatively Impacts Microvascular Function in Women with Endometriosis

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PURPOSE: Women with endometriosis are at an increased risk of developing cardiovascular disease and demonstrate impaired microvascular function, characterized by reduced nitric oxide (NO)-mediated vasodilation. Endometriosis is a systemic inflammatory disease in which NFκB-mediated cytokine production is upregulated. In clinical cohorts, NFκB inhibition with nonacetylated salicylate (oral salsalate) improves endothelial function. However, the effect of salsalate treatment in women with endometriosis is unknown. We hypothesized that NFκB inhibition with salsalate would improve cutaneous microvascular endothelial function in women with endometriosis. **METHODS:** In a single-blind, randomized, placebo-controlled design two intradermal microdialysis fibers were placed in the forearms of 7 women (34 ± 6.5 years) with laparoscopically diagnosed endometriosis. Local heating units were placed on the skin covering the microdialysis fibers and clamped at 33°C. Laser-Doppler flowmetry probes were placed within the heaters to measure red blood cell flux. Increasing doses of acetylcholine (ACh; 10^{-10} to 10^{-1} M) dissolved in lactated Ringer's solution were perfused through the fibers in 5-minute intervals. In one fiber, NO synthase was continuously inhibited with N^G-nitro-L-arginine methyl ester (15mM L-NAME). At the conclusion of the dose response, maximal vasodilation was induced (local heat to 43°C and 28mM sodium nitroprusside). Data were normalized as a percentage of maximal cutaneous vascular conductance (%CVC_{max}: flux/mean arterial pressure). NO-dependent vasodilation was calculated as the area between the Ringers and L-NAME sites and EC50s were calculated. Participants were tested after 5 days of salsalate (3000 mg/day) and placebo treatments. **RESULTS:** %CVC_{max} during Ach perfusion was decreased following salsalate treatment (site*treatment $p < 0.01$). NO-dependent vasodilation was also reduced following salsalate (291.4 AU v. 78.81 AU, respectively $p = 0.02$). The EC50 of the %CVC_{max} response to ACh was increased in the L-NAME site following placebo (logEC50 -4.936 M vs -2.081 M, respectively, $p < 0.01$), but not altered with salsalate treatment (logEC50 -3.150 M vs. -3.032, respectively, $p = 0.25$). **CONCLUSION:** NFκB inhibition with salsalate treatment impairs NO-mediated vasodilation in the cutaneous microcirculation in women with endometriosis. **SIGNIFICANCE/NOVELTY:** Endothelial dysfunction in women with endometriosis does not appear to be mediated through traditional inflammatory NFκB mechanisms. Other sources of NO including from inducible NO-synthase may be and upregulated as a compensatory mechanism in women with endometriosis. Supported by NIH Grant R01 HL16100