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Decreased endothelin converting enzyme-1 and neprilysin expression contributes to vascular dysfunction with Inflammatory Bowel Disease

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Inflammatory Bowel Diseases (IBD) are associated with poor intestinal perfusion and cardiovascular disease risk. Mesenteric arteries (MAs) increase blood flow via activation of perivascular sensory nerves and release of Calcitonin Gene-Related Peptide (CGRP) and Substance P (SP). Previous work highlights that CGRP and SP fail to dilate MAs during IBD. The metalloproteases endothelin-converting enzyme-1 (ECE) and neprilysin (NEP) control degradation and recycling of CGRP and SP receptors in many tissues, but their role in vasculature and IBD is unclear. Thus, we tested the hypothesis that IBD alters the expression and/or localization of ECE and NEP in MAs. IBD developed over 90 days in IL10-/- mice following *H.hepaticus* gavage, and C57BL6/J mice served as controls. To measure vascular expression/localization of ECE and NEP relative to CGRP and SP receptors, MAs were cannulated, pressurized labeled for ECE, NEP, CGRP (receptor activity modifying protein 1, RAMP1) and SP (Neurokinin 1, NK1) receptors before and after incubation in CGRP and SP to simulate sensory nerve activation. Ongoing work focuses on quantitative analysis of these 3D images. To verify clinical relevance, immunolabeling studies were repeated on vascular sections of human control and IBD colon samples. Resulting images were analyzed for area fraction fluorescent for ECE, NEP, RAMP1 and NK1 using ImageJ, with statistical analysis by nested t-tests. IBD was associated with decreased vascular expression ($P<0.05$) of NEP (Control 70±3%; IBD 41±5%), ECE (Control 74±2; IBD 51±3) and RAMP1 (Control 69±2%; IBD 57±3%), while NK1 was unchanged (Control 33±3%; IBD 28±2%). Decreased vascular expression of ECE, NEP and RAMP1 suggests decreased receptor recycling, which may contribute to inflammation and impaired sensory vasodilation with IBD. Further analysis of confocal images from mouse MAs will provide more information about how IBD affects CGRP and SP receptor trafficking and degradation as they relate to blood flow through mesenteric arteries.