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Role of Endothelin Converting Enzyme-1 and Neprilysin in Perivascular Sensory Nerve Dysfunction with IBD

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Inflammatory Bowel Diseases (IBD) are chronic diseases that are diagnosed in around 70,000 Americans each year, and 1.6 million Americans in total. IBD is closely associated with cardiovascular complications, including arterial stiffening and ischemic heart disease. Blood flow to the intestines is impaired with IBD, and dilation of the mesenteric arteries is facilitated by perivascular sensory nerves, through the release of calcitonin gene related peptide (CGRP) and substance P (SP). Previous experiments suggest that CGRP and SP receptors function abnormally and fail to facilitate artery dilation during IBD. To study those pathways further, we looked at two components of the CGRP and SP signaling pathways. The metalloproteases endothelin-converting enzyme-1 (ECE) and neutral endopeptidase (NEP) are very important to the GCRP and SP pathways because they control the degradation and the recycling of CGRP and SP receptors. My preliminary experiments yielded two major results: (1) decreased ECE and NEP content in mesenteric arteries with IBD and (2) colocalization of surface and internalized CGRP and SP receptors with both ECE and NEP in isolated smooth muscle cells from mesenteric arteries. Therefore, we hypothesize that that IBD decreases receptor and metalloprotease colocalization and internalization after sensory nerve stimulation, leading to decreased receptor recycling and impaired sensory vasodilation. We also predict that IBD decreases the effect of NEP and ECE inhibition on sensory vasodilation in intact, cannulated arteries. To test these hypotheses, C57BL/6, IL10-/- mice will be inoculated with Helicobacter hepaticus by gastric gavage after weaning and develop IBD over 90 days. Non-gavaged C57BL/6 mice will serve as controls. Confocal imaging (Leica TCS SP8) of cannulated, immunolabeled mesenteric arteries will determine how IBD affects CGRP/SP receptor recycling and NEP/ECE expression and localization after exposure to one or both neuropeptides. In separate experiments, pressure myography will be used to examine how IBD affects the role of ECE and NEP in vasodilation of live vessels. Sensory vasodilation will be measured before and after pharmacological blockade of one or both metalloproteases. Myography data will be analyzed via GraphPad Prism. Previous studies suggest that CGRP and SP signaling and receptor trafficking is altered specifically in blood vessels (mesenteric arteries and aorta) and their directly adjacent tissues (perivascular adipose and serum). If results indicate that IBD alters the role of NEP and ECE expression and activity in sensory neurotransmitter signaling and vasodilation, targeting ECE and/or NEP activity in IBD patients may have the potential to eventually improve both blood flow and intestinal function.

Life Sciences