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**ENTEROENDOCRINE CELLS AND APPETITE  
DYSREGULATION IN CROHN'S DISEASE**

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**Introduction** Loss of appetite and malnutrition in active Crohn's disease (CD) are important problems. The biological mechanisms underpinning appetite loss are unclear. Enteroendocrine cells (EEC) form a pivotal part of the brain-gut axis that controls appetite and satiety. They secrete gut hormones such as glucagon like peptide-1 (GLP-1) and polypeptide YY (PYY) which act on appetite control centres in the brainstem through an endocrine or paracrine pathway. Recent animal research has suggested that immune-regulated upregulation of proximal CCK-secreting EEC plays a mechanistic role in the appetite and feeding disturbance observed during gut inflammation. We have studied whether distal ileal EEC are perturbed in ileocolonic Crohn's disease.

**Methods** Patients with active intestinal inflammation were studied: active small and large bowel (SB and LB, respectively) CD and age/sex matched controls. Patient symptoms were assessed using a validated visual analogue score (VAS). At tissue level EEC markers and transcription factors have been studied through immunohistochemistry and quantitative polymerase chain reaction. Gut hormone responses to a test meal (PYY and GLP-1) were studied using a multiplex-ELISA technique.

**Results** CD patients with active inflammation displayed a ~6-fold significant reduction in appetite parameters as measured by VAS ( $p < 0.0001$ ). At the tissue level, the general EEC marker chromogranin A showed a 1.8-fold increase in positive cells ( $p = 0.01$ ), while GLP-1 cells were increased 2.5-fold in SB CD ( $p = 0.04$ ). PYY cells showed no change in number. Phox2b, a neural transcription factor associated with CD in a recent genome wide association study, was co-localised to EEC through dual immunofluorescence and showed a 1.5-fold increase in SB CD compared to controls. At mRNA level, significant increases were noted for Chromogranin A (3.3-fold;  $p = 0.009$ ), GLP-1 (2.7-fold  $p = 0.05$ ), Ubiquitination protein 4a (Ube4a) (2.2-fold  $p = 0.02$ ) but not PYY. Neurogenin 3, a NOTCH transcription factor central to EEC differentiation also showed ~2-fold-upregulation ( $p = 0.04$ ). In plasma, total PYY showed a 2-fold increase in postprandial levels in the SB-CD group compared to controls ( $p = 0.038$ ). It was not elevated in LB-CD. Active GLP-1 levels were, however, not elevated.

**Conclusion** Measurable changes were observed in distal small intestinal EEC markers in active CD, including elements of both GLP-1 and PYY. These data support a potential role of EEC in appetite dysregulation in intestinal inflammation. Measurements of gut hormones in peripheral blood may not adequately reflect biologically important changes occurring at the epithelial level. Enhanced EEC responses to nutrients may adversely affect appetite through increased gut-brain signalling, and provide novel therapeutic targets. Further work is underway to further dissect this neuroendocrine circuitry.

**Competing interests** None.

**Keywords** appetite, enteroendocrine.