Published in final edited form as:
Am J Gastroenterol. 2012 March ; 107(3): 448–450. doi:10.1038/ajg.2011.465.

Fecal Granins in IBS: Cause or Indicator of Intestinal or Colonic Irritation?

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Abstract

Ohman *et al.* report increased fecal granins in patients with irritable bowel syndrome (IBS). Several interesting questions arise from their observations. Are the granins a cause of the pathophysiology or phenotype in IBS? Is the elevation of granins specific to IBS? What is the cause of increased fecal granin levels? Can fecal granin levels be used to diagnose IBS? Are increased fecal granins an expression of intestinal or colonic irritation? This paper adds to the body of evidence suggesting there are gastrointestinal disturbances in IBS; understanding these disturbances may provide clues to its pathogenesis and optimize management.

In this issue of the journal, the study from Ohman *et al.* (1) assessed the associations between fecal levels of chromogranin (Cg) A and B, and secretogranin (Sg) II and III, with the clinical and pathophysiological phenotype of irritable bowel syndrome (IBS) patients. The results showed that, compared with healthy controls, IBS patients (70 of 85 having IBS-diarrhea (IBS-D) or alternating bowel function (IBS-A)) demonstrated higher levels of fecal CgA, SgII, and SgIII, but lower levels of CgB. There were strong negative correlations between the colonic transit time and fecal levels of CgA, SgII, and SgIII. Thus, faster colonic transit or lower colonic transit time was associated with higher fecal CgA, SgII, and SgIII levels. Associations between the granins and symptoms were weak, and the estimated contribution (R^2) of granins to the abdominal pain and stool frequency, anxiety and depression accounted for < 10 % of the variance of these symptoms. The authors appropriately discuss that these are hypothesis-generating data, given the very large numbers of comparisons and associations sought, and the numbers of IBS patients (n=85) and healthy controls (n=29) included. The data require replication and larger sample sizes. However, these intriguing data raise several questions:

First, do these data support the granins as a cause of the pathophysiology or phenotype in IBS? It is conceivable that the several bioactive peptides that could be released from the granins by precursor-processing enzymes may result in pathophysiology of IBS. However, several of the biologically active peptides encoded within the CgA molecule, such as vasostatin, beta-granin, chromostatin, pancreastatin, and parastatin, function predominantly to inhibit hormone and neurotransmitter release in an autocrine or paracrine manner (2), and would not be expected to induce accelerated transit or diarrhea in IBS. On the other hand, granins released into the intestinal lumen and appearing in feces may serve as biomarkers of

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Guarantor of the article: Michael Camilleri, MD.

Potential competing interest: None.

the release of other bioactive substances such as serotonin, just as serum CgA serves as a biomarker of the release of serotonin in patients with carcinoid tumors.

A causative relationship between the granins and IBS would require an intervention to modify the biochemical factors and observe a change in phenotype. No such intervention was reported. Hence, the study design cannot differentiate whether the increased fecal granins cause IBS or its symptoms, or merely reflect the phenotype of IBS, such as the alteration in oroanal transit or bowel function. The patient cohort was predominantly IBS-D and IBS-A. In a scintigraphic colonic transit study of 120 patients with IBS, 46% of IBS-D, and 17% of IBS-A had accelerated colonic transit at 24 or 48 h (3). Indeed, the negative correlation of colonic transit time and levels of CgA, SgII, and SgIII suggests that the increased fecal granins may result from the accelerated transit. A prior study had also demonstrated transient elevation of serum CgA levels in a minority of patients with IBS-D (4). It is reasonable to assume that increased serum CgA in the latter study reflected increased granin release from gastrointestinal enteroendocrine cells.

Second, is the elevation of granins specific to IBS? There was no disease control group in this study, which cannot, therefore, address the specificity of the increased fecal granins. The literature suggests that increased fecal granins are unlikely specific to IBS as other diseases are associated with increased Cgs, including lymphocytic colitis, which is associated with increased Cg cell density in the colon (5), and celiac disease (6,7). Chromogranin A is a very sensitive marker that reflects tumor load in various types of neuroendocrine tumors (8) and is elevated in carcinoid diarrhea, which may present with symptoms that mimic IBS-D.

Third, what is the cause of increased fecal granin level? Does it represent enteroendocrine hyperplasia as observed for serotonin- or Cg-expressing enteroendocrine cells in celiac disease (6,7), or the increased number of enteroendocrine cells documented in IBS, especially post-infectious IBS (9,10)? Or does the arrival of intraluminal chemicals into the colon stimulate the release of products of enteroendocrine cells into the lumen? This could be analogous to the release of 5-hydroxytryptamine from human enteroendocrine cells in response to bile salts, amines, tastants, and olfactants (11,12). The latter hypothesis is consistent with the observation that accelerated oroanal transit, which may result in malabsorption of endogenous chemicals (e.g., bile acids and proteases) or delivery of products of digestion to the colon, is associated with higher fecal granin levels. Although the authors interpret this association to indicate that the increased fecal granins may cause the accelerated colonic transit, the current studies do not prove this, and the alternative explanation that accelerated transit increases fecal granin levels is, at least, equally tenable. Indeed, this is consistent with the hypothesis that factors present in the intestinal lumen may alter its function, causing an “irritated colon”, a concept introduced by Painter (13) to explain the effects of fiber-deficient diets containing much refined carbohydrate.

What do we know about the concept of irritated colon? Although the observations in the literature do not specifically address the release of granins as a manifestation of irritation, analogies can be drawn with the release of other chemicals from enteroendocrine cells such as serotonin, or the pathophysiological responses triggered by the presence of luminal factors that may also serve as irritants (14). These include exogenous dietary components and, possibly, endogenous chemicals involved in the digestive process. Malabsorbed sugars, such as lactose, may mimic the features of IBS (15); a Norwegian case–control study suggested that IBS and lactose malabsorption were separate entities (16). Fructose and sorbitol malabsorption have also been observed in Danish patients with IBS (17), but the prevalence of malabsorbers among one group of patients with IBS in the Netherlands was similar to that in healthy controls (18). Dietary gluten intolerance may also occur in patients

with IBS, and those who respond to gluten withdrawal may be genetically susceptible to the effects of gluten (19).

The ileum of patients with IBS is excessively sensitive to the secretory effects of perfused bile acids (20). Ileal malabsorption of bile acids may induce cholerrheic enteropathy with diarrhea (21); in a systematic analysis of the literature, Wedlake *et al.* (22) estimated that bile acid malabsorption may account for about 30% of patients with unexplained functional diarrhea that has significant overlap with IBS-D. Short- or medium-chain fatty acids reach the right colon in patients with borderline absorptive capacity or rapid transit in the small bowel. In healthy volunteers, 2–20% of dietary starch escapes absorption in the small bowel (23), providing substrate for the generation of short-chain fatty acids by colonic bacteria. Short-chain fatty acids initiate high-amplitude–propagated contractions in the colon, propelling colonic content rapidly and, possibly, resulting in pain or diarrhea (24,25). The short-chain fatty acid receptor, GPR43, is expressed by enteroendocrine cells and mucosal mast cells in rat intestine (26). Short-chain fatty acids stimulate colonic transit via intraluminal 5-hydroxytryptamine release in rats; propionate-induced responses were not observed in mucosa-free preparations, suggesting that propionate acts on receptors in the mucosa, causing the release of 5-hydroxytryptamine from enterochromaffin cells (27,28). The FODMAP (Fermentable Oligo-, Di- and Mono-saccharides and Polyols) approach to management of functional gastrointestinal symptoms is geared to reducing stimulation of colonic contractility and secretion by restricting the production of short-chain fatty acids (29).

Fourth, what is the origin of the granins? The authors argue convincingly that it is not the neutrophils and suggest it might be the enteroendocrine cells or mast cells. Granins are produced by and secreted from mast cells. Although many papers document increased numbers of mast cells in mucosal biopsies from IBS patients, other studies do not confirm this (reviewed in ref. (30)).

Given the large number of enteroendocrine cells and their exposure to luminal content, it is likely that, at least in part, the granins originate from enteroendocrine cells. In fact, the clearest expression of elevated granins occurs in patients with neuroendocrine tumors that arise in enteroendocrine cells.

Fifth, can fecal granin levels be used to diagnose or treat IBS? The study lacks the positive disease control groups to address the potential of fecal granins as a diagnostic test. The lack of specificity of fecal and serum Cgs, which are elevated in lymphocytic colitis, celiac disease, and carcinoid diarrhea, implies that the differences observed in fecal granin levels between IBS and healthy controls do not support the use of fecal granins as a positive biomarker for IBS. On the other hand, elevation of fecal granins may serve as a marker for the involvement of endogenous transmitters that may be causing the bowel dysfunction and provide additional rationale for treatment with octreotide of debilitating chronic diarrhea that is refractory to first-line drugs and requires intravenous fluids or repeat hospitalizations (31).

Sixth, what is the potential role of the released granins? Chromogranins / secretogranins are present in secretory vesicles of nervous, endocrine, and immune cells. In chromaffin cells, activation of nicotinic cholinergic receptors induces the release, with catecholamines, of bioactive peptides resulting from a natural processing. New antimicrobial Cg-derived peptides have been identified in the secretions of stimulated bovine chromaffin cells. They function at the micromolar range against bacteria, fungi, and yeasts, and are nontoxic for the mammalian cells themselves (32). It has also been demonstrated that CgA can induce the formation of mobile secretory granules and promote the sorting and release of peptide hormones from enteroendocrine cells (33).

In summary, the paper of Ohman *et al*. (1) generates intriguing hypotheses and raises many important questions. There are many potentially important mechanisms of gastrointestinal dysfunction that need to be sought, understood, and treated in IBS patients. IBS is not all in the head.

Acknowledgments

Financial support: No financial support was given to this project. Camilleri received NIH funding to study bile acid malabsorption in irritable bowel syndrome (NIH RO1 DK-092179).

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