

Autacoids in Inflammatory Bowel Diseases

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Editorial

Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis (UC), are complex disorders characterized by chronic, local and systemic inflammation and spontaneously relapsing course. The causes of these diseases are unknown, however they display genetic and environmental components and appear to be immunologically mediated in part by enteric microbiota [1]. The immune system cells activation may lead to activation of plasma proteolytic cascades [1,2], as well as to release of inflammatory mediators in inflamed intestine. There are convincing evidences that IBD are diseases of immunological hyperresponsiveness within the mucosa. Immunological reactions may be directed against luminal bacteria and their products normally present in the intestine [2]. Both innate and adaptive immune response play a role in IBD pathogenesis and possibly in etiology. Autacoids, a local hormones e.g., histamine, serotonin, kinins, angiotensin, eicosanoids, neurotensin, nitric oxide, endothelins may be produced and act locally in IBD – inflamed intestine, and play a role inflammatory response, and progression in both Crohn's disease and UC. A role of eicosanoids and nitric oxide in IBD was relatively well delineated. Much less attention has been paid to other autacoids, although a significance of the intestinal tissue kallikrein – kinin system in IBD has been investigated in the late 1990s – 2000s. Histamine, serotonin and kinins are vasodilator autacoids which as part of the humoral defense system participate in the inflammatory response. Enterochromaffin cell- which are present in the mucosa of all regions of the gut except the oesophagus, contain most of the body's serotonin (5-HT). Derived serotonin (5-HT) express toll-like receptors and thus may detect microorganisms [3,4]. Enterochromaffin cell 5-HT also appears to contribute to the initiation of intestinal inflammation, at least in the animal models. Mice that lack the 5-HT transporter (SERT; SERTKO mice), which inactivates 5-HT, are sensitive to experimentally induced colitis especially in animals with interleukin (IL)-10 deletion [5,6]. Histamine as a proinflammatory mediator is selectively located in the granules of human mast cells and basophils and released from these cells upon degranulation. It was shown that the number of mast cells and mast cells tryptase expression (a marker of mast cell degranulation are increased in colonic mucosa and submucosa in experimental and human IBD [7]. Interestingly, mast cells originated from the resected colon of active Crohn's disease or UC released more histamine than those from normal colon after stimulation with colon-derived murine epithelial cell-associated compounds [8]. Knutson et al. found that the histamine secretion was increased in patients with Crohn's disease compared with normal controls, and the secretion of histamine was related to disease activity, indicating strongly that degranulation of mast cells was involved in active Crohn's disease [9].

A significance kinins in human IBD is still underestimated although in animal IBD models kinins have been documented in part to mediate intestinal and systemic inflammation. Tissue kallikrein cleaves kininogens to release kinins. The importance of intestinal tissue kallikrein (ITK) in the intestine mainly depends upon the secretion of active enzyme in the presence of kininogens, especially low molecular weight kininogen (LK), with subsequent kinins generation. It should be noted that in mild insults, kinins may play a salutary role recruiting to the extravascular milieu proteases, acute phase proteins, and neutrophils. In severe inflammation, however, kinins amplifies the inflammatory cascade, and contributes to tissue destruction. In late 1990s we have focused our attention on the ITK-kinin system in IBD. To study the localization of ITK and its naturally occurring serine protein inhibitor (SERPIN), kallistatin, in IBD we first focused in our models of rats enterocolitis induced by proteoglycan-polysaccharide (PG-APS) closely resembling Crohn's disease [10]. We showed that the normal location of ITK was the goblet cells and that substantial amounts of ITK were present in the macrophages of the granuloma found in the submucosa, suggesting that ITK is present at the site of inflammation. In addition, ITK was found to be lower in the supernatant from in vitro cultures of inflamed intestine. This combination suggested secretion of ITK during inflammation.

In the human studies [11,12] related to ITK – kallistatin we also observed a colocalization of ITK and kallistatin proteins in the endothelium of intestinal vessels, and in macrophages forming granuloma, indicating the significance of ITK related pathway in Crohn's inflammation. This observation emphasizes the close relationship between the immune responses important in IBD and the inflammatory mediators including the kallikrein-kinin system. Similar results have demonstrated Devani et al. [13], and both our's and Devani's results indicate that depletion of ITK as well as kallistatin is related to degree of intestinal-IBD. Importantly activated basophils and mast cells contain and may release kallikrein as an additional local intestinal source of tissue kallikrein [14] which may indicate a significance of innate immune system related to intestinal tissue kallikrein – kinin pathway in IBD.

Later in 2000s in human studies we demonstrated the increase in the ratio of bradykinin receptors B1 and B2 e.g. B1R to B2R gene expression in relation to the degree of intestinal inflammation, and visualized both B1R and B2R in normal as well as inflammatory human colon and ileum [15]. We evaluated the distribution of bradykinin receptors in human intestinal tissue in patients with IBD showing that both B2R and B1R proteins are expressed in the epithelial cells of normal and IBD intestines. B1R protein is visualized in macrophages at the center of granulomas in Crohn's disease. B2R protein is normally present in the apices of enterocytes in the basal

area and intracellularly in inflammatory tissue. In contrast, B1R protein is found in the basal area of enterocytes in normal intestine, but in the apical portion of enterocytes in inflamed tissue. B1R protein is significantly increased in both active UC and CD intestines compared to controls. In patients with active UC, B1R mRNA is significantly higher than B2R mRNA. However, in inactive UC patients, the B1R and B2R mRNA did not differ significantly. Thus, bradykinin receptors in IBD may reflect intestinal inflammation. Increased B1R gene and protein expression in active IBD provides a structural basis of the important role of bradykinin in chronic inflammation. Latter Hara et al. [16] shown that upregulation of B1R in the trinitrobenzene sulphonic acid (TNBS) – induced colitis model is in part dependent on NF- κ β activation. Kininogen has been demonstrated in both normal and inflamed human colon, thus, ITK can generate kinins. In addition, kallistatin, a major tissue kallikrein inhibitor and kininase II, a kinin inactivator, have been demonstrated in intestinal tissue [11]. Our data from human study showing alteration in distribution of BR1 and significantly increased its levels in the patients with IBD tend to corroborate with experimental Hara et al. results suggesting that selective B1R receptor antagonist may have potential in therapeutic trial. It should be noted that kinins are implicated in the regulation of blood pressure, sodium homeostasis and the cardioprotective effect of preconditioning. Angiotensin-converting enzyme (kininase II) inhibition increase blood levels of bradykinin and kallidin peptides [17]. Thus, the potentially salutary role of kinins in the circulation not encourage systemic administration of B1R antagonist. Recently Marceau and Regoli [18] suggested that topical drug delivery to intestine as for 5 – ASA compounds to avoid side effect may be appropriate for the management of IBD.

What is the role of the ITK – kinin system in the inflamed colon? The importance of ITK in the intestine mainly depends upon the secretion of active enzyme in the presence of kininogens, especially LK, with subsequent kinins generation ITK apart from its kininogenase activity, it has been implicated in the processing of growth factors and peptide hormones. Tissue kallikrein hydrolyze vasoactive intestinal peptide and procollagenase in vitro. If these reactions take place in IBD, ITK may influence intestinal motility, secretion and connective tissue metabolism. Kinins not only have many proinflammatory actions, as a mediator of inflammation, responsible for pain, vasodilation, and capillary permeability, but also may stimulate release of mediators for endothelial, epithelial, and white blood cells, such as thromboxanes, nitric oxide, and cytokines, and promote adhesion molecule – neutrophil cascade known to be important in IBD. Receptors for these reactions are present in the human intestinal epithelium and, thus, kinin can initiate these inflammatory reactions in the inflamed ileum and colon. Thus further investigation concerning a role of the ITK – kinin system and other autacoids in experimental and human IBD is worth to pursue.

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