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REVIEW

# Even low-grade inflammation impacts on small intestinal function

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## Abstract

Independent of the cause and location, inflammation - even when minimal - has clear effects on gastrointestinal morphology and function. These result in altered digestion, absorption and barrier function. There is evidence of reduced villus height and crypt depth, increased permeability, as well as altered sugar and peptide absorption in the small intestine after induction of inflammation in experimental models, which is supported by some clinical data. Identification of inflammatory factors which may promote the process of gastrointestinal dysfunction as well as clinical research to verify experimental observations of inflammatory modulation of gastrointestinal function are required. Moreover, nutritional strategies to support functional restitution are needed.



**Key words:** Small intestine; Digestion; Absorption; Motility; Permeability; Low-grade inflammation; Cytokines

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## INTRODUCTION

The gut mucosa is a highly organized structure that is adapted to the absorption of dietary components from the gastrointestinal lumen. It is maintained by a critical balance between epithelial cell proliferation, differentiation, migration and apoptosis[1]. A complex interplay between multiple signaling events within epithelial cells controlling extracellular signals either from neighboring cells (cell-cell or cell-matrix contacts) or from a distant origin (e.g. hormones) maintains the specific organization and function of these cells.

Inflammation, regardless of its location or extent, sends many local and systemic signals, which in turn may cause changes in the intestine. Inflammation alters the metabolic status and elevates energy expenditure, fat metabolism and protein catabolism[2,3]. The intestine, however, has an inherent ability to adapt morphologically and functionally in response to internal and external environmental stimuli[4]. The adaptations include modifications of the brush border membrane fluidity and permeability as well as up- and down-regulation of carrier-mediated transporter proteins.

Inflammatory processes initiate a cascade of intestinal events which not only influence the mucosa itself but may also affect the function and integrity of remote organs and tissues. Interleukin-1β (IL-1β), for example, has both direct central and indirect peripheral depressant effects on appetite mechanisms, whereas plasma concentrations

of tumor necrosis factor α (TNF-α) are associated with increases in energy expenditure[5,6]. Lymphocyte activation leads to increased glucose consumption which stimulates major glucose-transporter proteins (GLUT) and insulin receptors[7,8]. Increased expression of insulin receptors is essential for immune cell division, size and survival, and IL-7 seems to be essential in this process[9].

This review gives a brief overview of some observations of the morphological and functional changes in the non-inflamed part of the small intestine that are caused by inflammatory events in other parts of the body.

## MORPHOLOGICAL ALTERATIONS IN THE INTESTINAL MUCOSA

Gastrointestinal dysfunction is a common complication in patients with traumatic brain injury (TBI)[10]. It is proposed that TBI sets off a sequence of local and systemic inflammatory events. Hang *et al*[11,12] found increased TNF-α and IL-6 concentrations in the jejunal tissue of mice after parietal brain contusion induced by a weight-dropping method. In this TBI model, Hang *et al*[11] demonstrated rapidly developing histopathological damage of the gut mucosa, including apoptosis of epithelial cells, loss of tight junctions and mitochondrial damage. They found reduced jejunal villus height, crypt depth and surface area as early as 3 h following induction of brain injury.

Morphological alterations have been confirmed in rats. Chen *et al*[13] induced TBI by a weight-dropping method in male Wistar rats. Ileal tissue was analyzed 5 d after brain injury. The villus height and crypt depth of ileal samples were significantly decreased compared to healthy controls. The authors also noticed increased inflammatory markers, such as IL-1β, TNF-α, IL-6 and intracellular adhesion molecule-1 expression, in the ileal tissue.

Sundaram *et al*[14] found similar alterations in the mucosal structure in the non-inflamed part of rabbit ileum after colitis induced by intragastrically inoculated microbes. Despite a clear increase in proinflammatory IL-10 in duodenal, jejunal and ileal tissue samples, however, neither Barada *et al*[15] nor Mourad *et al*[16], observed any histological alterations in the non-inflamed small intestine of colitis-induced rats. Colitis was induced by intracolonic administration of iodoacetamide or 2,4,6-trinitrobenzene sulfonic acid.

Morphological alterations in the small intestine in inflammatory bowel disease (IBD) patients are conflicting. Whereas Salem & Truelove[17] and Arvanitakis[18] found histological changes in the non-inflamed part of the jejunum in almost 70% of IBD patients, Soulé *et al*[19] only observed morphological abnormalities in less than 5% of patients.

In chronic heart failure patients, the presence of endothelial dysfunction is associated with increased levels of inflammatory markers[20]. This may also induce morphological changes in the intestine. Sandek *et al*[21] reported thickening of non-inflamed ileal walls and of all parts of the large intestine in chronic heart failure patients compared with control subjects of similar age. The increase in wall thickening was about 30% in the terminal ileum and almost 50% in the transverse colon. Increased bowel wall thickness in the small intestine is a frequent finding in various inflammatory-related conditions, such as acute ischemic colitis, IBD and food hypersensitivity[22,23].

To summarize, many of the above-mentioned studies in animal models assume the contributory effects of inflammatory mediators to be, at least partly, behind the observed morphological changes in the small intestine. However, there is no clear opinion as to the degree or location of inflammation or the quantity or quality of morphological changes in the small intestine. In addition, the possible route of effects, whether e.g. *via* circulating mediators or the autonomic nervous system, remains to be clarified.

## ALTERATIONS OF PERMEABILITY

Tight junctions are dynamic structures that limit the passive absorption of hydrophilic molecules from the intestinal lumen, thereby being crucial in intestinal barrier mechanisms.

Proinflammatory cytokines IL-1β and TNF-α increased epithelial tight junction permeability *in vitro* in Caco-2 cells dose- and time-dependently[24,25]. This was mediated by an increase in myosin L chain kinase (MLCK) expression and activity, which in turn was mediated by a nuclear factor-κB-dependent increase in MLCK gene transcription[26,27]. In a rabbit jejunal *ex vivo* model, however, added IL-8 had no effect on passive tissue permeability measured with Cr-EDTA in Ussing-type chambers[28]. Nevertheless, cytokines affected neurotransmitter release and content, suggesting the leading role of the autonomic nervous system[29].

Intestinal mucosal function can be assessed *in vivo* by measuring the permeability of the mucosal barrier to small or large solutes as in a lactulose-mannitol test. Mannitol (M), a small sugar, passes through the cell membranes. Lactulose (L), a large molecule, is absorbed paracellularly through the tight junctions. Increased absorption of lactulose can reflect mucosal leakiness, and decreased absorption of mannitol can indicate a decreased functional absorptive area. In a rat model of TBI, the L/M ratio increased significantly at 3 h following brain contusion and reached a peak level at 72 h, indicating rapidly increased permeability and disruption of tight junctions between epithelial cells[11].

Feighery *et al*[30] measured ileal permeability *ex vivo* in Sprague Dawley rats after inducing brain injury. After cortical contusion, ileal segments were removed and mounted in Ussing chambers within 30 min. Significantly reduced ileal barrier function was observed by monitoring fluxes of C-mannitol crossing epithelial tight

junctions. The authors assumed this to be mediated by opening of the tight junctions caused by disturbances in the autonomic nervous system or possibly also by hemorrhagic shock. In addition, cerebral stroke leads to immunodepression promoting gut barrier dysfunction, which has led to increased permeability in a mouse model[31].

In a colitis rat model, Fries *et al*[32] found leaky tight junctions in the non-inflamed duodenum and ileum where permeability was increased over 70% compared with healthy controls. This increase correlated positively with the macroscopic colon damage score. In this study, colitis was induced by intrarectal trinitrobenzene sulfonic acid. Changes in the permeability of the non-inflamed part of the small intestine have been previously noticed in Crohn's disease (CD) patients[33]. Söderholm *et al*[34], however, found no changes in baseline permeability in surgical segments of non-inflamed distal ileum of CD patients. In spite of this finding, intestinal tight junctions of CD patients were noticed to be more reactive to luminal stimuli of sodium caprate (a constituent of milk fat affecting tight junctions) compared with ileal segments from colon cancer patients, who served as non-inflamed controls. The authors assumed that the altered function of the small intestinal tight junctions was mediated *via* disturbed cytoskeletal contractility in inflamed patients.

Chronic heart failure patients showed a 35% increase in small intestinal permeability measured by the L/M test and a 29% decrease of D-xylose absorption, which reflects a reduced activity of passive carrier-mediated transport[21]. This may be due to diminished gut circulation contributing to local edema and leading to reduced barrier function and dysfunction of transport proteins, but proinflammatory cytokines can also influence gut epithelial hyperpermeability. Furthermore, the possible effect of long-term medication cannot be excluded with these patients.

To sum up, increased permeability has been noticed in many experimental animal models of inflammation, which is supported by some clinical observations. Altered permeability is most likely mediated by open tight junctions, but the role of inflammatory agents and the autonomic nervous system in this phenomenon remains to be studied. Changes in the barrier function may have implications for nutrient absorption as well as for multiple organ failure caused by increased systemic delivery of luminal endotoxins.

## ALTERATIONS OF INTESTINAL MOTILITY

Gastrointestinal motility is regulated by circulating and local hormones as well as neurotransmitters, mainly of the enteric nervous system. Release of these agents, however, is regulated by the central nervous system (CNS). Brain-gut peptides, such as cholecystokinin (CCK), vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP), are important mediators in the regulation of gastrointestinal motility. Several kinds of stress, such as trauma, cold, and pain, can induce the release of these peptides from the CNS and enteric nerves[35]. Even psychological stress inhibits small intestinal motility by regulating the expression of CCK and VIP[36].

Evidence of inflammatory impact on gut motility and gastrointestinal transit is scarce. However, Hang *et al*[37] measured gastric distension, delayed gastric emptying and intestinal dilatation in rats after brain contusion induced by a weight-dropping method. They also noticed significant changes of brain-gut peptides CCK, VIP and CGRP both in plasma and jejunum tissue, which were assumed to be involved in the pathogenesis of gastrointestinal dysmotility due to systemic stress.

## ALTERATIONS OF NUTRIENT ABSORPTION

There is experimental and clinical evidence that intestinal inflammation is often associated with altered malabsorption of fluids, electrolytes and nutrients - in the inflamed as well as the non-inflamed parts of the intestine[16-18,33,38-40].

Lactose and sucrose are the major disaccharides in the human diet. Before absorption, they are hydrolyzed to monosaccharides by the microvillus membrane enzymes, lactase and sucrase. Luminal factors, hormones and growth factors regulate the expression of these enzymes along the longitudinal and vertical axes of the small intestine. The iodoacetamide-induced colitis model of Jurjus *et al*[41] showed a transient reduction in jejunal lactase and sucrase expression on days two and four after colitis induction in rats. The same observation was made for the jejunal aminopeptidase and GLUT-5 expressions. Aminopeptidases are involved in protein digestion in the jejunum and ileum, and GLUT-5 is a fructose transporter of the small intestine. The expression of lactase, aminopeptidases and brush border GLUT-5 returned to normal in the jejunum following the resolution of colonic inflammation. However, sucrase and crypt GLUT-5 expression remained lower for four or more days. Jurjus *et al*[41] suggest that the reduced enzyme expressions are probably due to decreased translation or increased degradation, or both, since transcriptional changes were not noticed. Previously, a significant reduction in disaccharidase activity in the jejunum and ileum of IBD patients has been noticed[18,33].

Chronic heart failure patients have reduced intestinal sugar absorption, determined by the follow-up of urinary recovery of orally administered D-xylose[21]. This indicates diminished absorption due to alterations in passive carrier-mediated transport. However, the effects of circulation and heart function cannot be excluded. There is also an increased risk of anemia among heart failure patients, but the mechanisms for this phenomenon are not entirely clear[42]. In addition to renal dysfunction and decreased renal blood flow, circulating neurohormonal

and proinflammatory cytokines appear to contribute to anemia in chronic heart disease.

Interleukins may modulate intestinal transport function. Some proinflammatory cytokines have been reported to exert significant effects on central and peripheral regulation of glucose metabolism, which may be related to the increased metabolic demands of inflamed tissue. IL-6, IL-1α and IL-8 seem to improve the absorption of glucose *ex vivo* in rabbit jejunal tissue[28]. Intracerebroventricular injection of IL-1α enhances whole-body glucose metabolism and increases insulin levels[43]. No alterations were seen after intravenous administration of the same dose. Anti-inflammatory IL-10 appears to have no role in the regulation of jejunal nutrient transport[28].

TNF-α is an important inflammatory mediator that plays a central role in triggering inflammatory reactions. Absorption of monosaccharide galactose in incubated rat intestinal rings is impaired by proinflammatory IL-1β and TNF-α by 30%[44]. In an experimental model of sepsis, intravenous administration of TNF-α inhibited intestinal D-fructose absorption in the rabbit jejunum by decreasing the expression of the GLUT-5 transporter at the brush border membrane[45]. It also inhibited D-galactose transport across the apical membrane of the enterocyte in rabbit intestinal tissue preparations and brush border vesicles by reducing the amounts of $Na^+$/glucose cotransporter protein (SGLT1) in the plasma membrane through a mechanism in which several protein-like kinases are involved[46].

Proinflammatory cytokines IL-1α and IL-8 significantly increased L-proline absorption *in vitro* in the rabbit jejunal tissue[28]. However, in rats with intracolonic iodoacetamide-induced colitis, jejunal alanine absorption was reduced 30%-40% at two days following iodoacetamide administration[47].

Brain injury in a rat model increased the transport and uptake of dipeptides, even though the villus height and surface area were demonstrated to be significantly decreased[48]. This process was carried out by increases in the intestinal brush border transporter PepT1, which transfers dipeptides from the intestinal lumen to enterocyte cytoplasm. Rat intestinal PepT1 can be up-regulated under the influence of many factors including the dietary protein load[49]. Up-regulation of this oligopeptide transporter in the intestine suggests that the gut can increase the luminal transport of dietary proteins in the form of di- and tripeptides during intestinal failure, independent of changes in the mucosal surface area. This has pharmacological implications as well, since PepT1 mediates the intestinal absorption of some peptide-like drugs[50]. There is some evidence that PepT1 may even have a role in inflammatory processes, since it is up-regulated in the colonic epithelial cells of patients with chronic ulcerative colitis and CD[51].

To summarize, the observations of changed absorptive capacity of the small intestine are mainly from animal models. Maldigestion of carbohydrates and changes in transporters of sugars and peptides have been noticed.

**Table 1 Summary of *in vivo* evidence of changes in small intestinal function induced by inflammation markers**

| Alterations in intestinal | Inflammation model | | |
|---|---|---|---|
| | TBI | IBD, colitis | Chronic heart failure with low-grade inflammation |
| Morphology | A, H | A?, H? | H |
| Permeability | A | A, H? | H |
| Motility | A | | |
| Absorption | A | A, H | H |

Most observations in this summary are, however, from a single study. TBI: Traumatic brain injury; IBD: Inflammatory bowel disease; A: Evidence from animal studies; H: Evidence from clinical studies; ?: Conflicting results.

The clinical relevance of these observations remains to be elucidated.

## CONCLUSION

Systemic or local inflammation may influence the intestinal absorptive area, epithelial cells, and barrier function *via* released inflammatory mediators and products from activated immune cells. Knowledge regarding the interplay of inflammation and intestinal function is scant. The molecular mechanisms of these changes may differ in acute and chronic inflammation.

Even if the number of observations of morphology, permeability, motility and digestion is limited, the results are interesting and indicate possible clinical relevance. Table 1 summarizes the existing *in vivo* evidence. Most of the observations, however, have been made after TBI which is an extreme model for studying inflammatory responses in the intestine. Interesting early clinical results of altered intestinal morphology and function have been obtained in chronic heart failure patients. Chronic heart failure is associated with increased levels of inflammatory markers related to so-called low-grade or minimal inflammation.

More research is needed to verify these mainly experimental observations and to establish their possible clinical relevance.

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