



Review Article

Impairment of Small Intestinal Function in Ulcerative Colitis: Role of Enteric Innervation

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Abstract

Small intestinal dysfunction has been described in patients with ulcerative colitis and in experimental animal models of colitis. This is demonstrated by a decrease in fluid, electrolyte, amino acid, fat and carbohydrate absorption as well as by deranged intestinal motility. Histopathological changes in the small intestines in colitis have not been consistently demonstrated, but there is evidence of structural and biochemical alterations as shown by increased intestinal permeability and a decrease in the expression of multiple brush border membrane enzymes such as disaccharidases and aminopeptidases, in both humans and experimental animals. The pathophysiology of this dysfunction has not been elucidated, but it is thought to include alterations in neural circuitry such as increased neuronal excitability, neuronal damage and changes of neuropeptidergic innervation and receptors as well as an increase in local production of pro-inflammatory cytokines and alterations in the production of some neurohumoral mediators. In the following, we provide an update on the advancement of clinical and scientific contributions to elucidate the underlying mechanisms of the alteration of the functions of apparently intact small intestinal segments, induced by ulcerative colitis.

Key Words: Ulcerative colitis; enteric nervous system; small intestinal dysfunction

1. Introduction

Chronic inflammatory bowel diseases [IBD], which include ulcerative colitis [UC] and Crohn's disease, encompass a wide spectrum of interactions between genetic predisposition, exogenous and endogenous triggers and modifying factors. These lead to increased intestinal permeability, which allows the translocation of bacterial antigens through the lumen of the gastrointestinal [GI] tract and leads to activation of immune cells and abnormal cytokine production.¹ The outcome of these processes leads to spontaneously relapsing and remitting inflammatory processes resulting in tissue injury. The latter is mediated by the immune system² with accumulation of different types of immune cells [neutrophils, macrophages etc.], in addition to increased levels of inflammatory cytokines including interleukins [IL] 1, 2, 6 and 8, and an increase in tumour necrosis factor alpha [TNF- α] and arachidonic acid metabolite levels.^{2–6} In addition, changes in the intrinsic and extrinsic innervation of the GI tract and

their interaction with the immune system have been shown to play a key role in the pathogenesis and in the propagation of inflammation as well as in the healing process.⁷ This can be illustrated by neuronal damage and loss of mucosal neuropeptidergic innervation.^{1,8,9}

Although Crohn's disease can affect any part of the gastrointestinal tract, UC is generally confined to the colon with occasional extension into terminal ileum in what is known as 'backwash ileitis'¹⁰ and with the rare occurrence of systemic toxicity with multiple organ dysfunction [MOD] in severe colitis.^{11,12} However, many studies have shown some functional abnormalities in the small intestine of patients suffering from UC as well as in experimental animal models of colitis. These abnormalities are manifested by a decrease in intestinal fluid, D-Xylose, amino acid and fat absorption.^{13–17} The pathophysiology of this decrease, however, has not been well elucidated. The discrete cross-talk between the colon and the small intestine could be the result of neuronal reflexes,

mediated through the release of cytokines or some other neuro-humoral factors. Some investigators reported histopathological changes in the jejunum of patients with UC.^{13,16} However, these findings were not confirmed by others.^{18,19} Interestingly, a subgroup of patients with UC is reported to have increased small intestinal permeability, which was more common in those with extensive disease, and which was present even during remission.²⁰ The aetiology of these abnormalities is not fully understood, and their contribution to the small intestinal dysfunction is not clear. In addition, it has been well established that patients with UC have increased prevalence of irritable bowel syndrome-like symptoms such as abdominal pain and diarrhoea even when the colitis is quiescent.²⁰⁻²³ This could be explained by the persistence of microinflammation in the mucosa and increased intestinal permeability.^{20,21} The fact that patients with IBD have a low cell mass index and may suffer from malnutrition and hypoproteinaemia²⁴ has been attributed to several factors, including: a decrease in food intake; a decrease in intestinal absorption of nutrients; a highly extensive catabolic state secondary to the chronicity of the inflammatory process; or a combination of these factors. The contribution of intestinal malabsorption to the low body weight has not been well studied and remains unknown. In this report we review the available evidence of small intestinal dysfunction in UC and the proposed underlying mechanisms.

2. Small intestinal dysfunction in colitis

2.1. Fluid and nutrient malabsorption

Several functional abnormalities have been previously described in the non-inflamed small intestine of some patients with ulcerative colitis. Using perfusion studies, a significant decrease in fluid and electrolyte absorption from human jejunum was demonstrated in patients with ulcerative colitis.¹⁴ In addition, impaired absorption of amino acids,²⁵ folic acid and fat as well as an abnormal D-Xylose test^{13,15,16,19,26} have been reported in humans [Table 1]. Even in remission, the colon may have altered secretory capacity as recently demonstrated by Gustafsson *et al.*²⁷ who found that proximal colonic mucosa is more sensitive to cAMP-dependent secretion and less sensitive to Ca²⁺-dependent secretion, which may contribute to persistent diarrhoea in these patients. On the other hand, the mRNA levels of the bile acid transporter were found to be decreased in the

ileum of patients with UC²⁸; however, there is no evidence that these patients develop bile acid malabsorption.

Animal models of chemical colitis have been widely used to study the pathogenesis of IBD and the effect of some novel therapies on colonic inflammation. Few studies have looked at small intestinal disturbances in these animal models of colitis. A decrease in ileal fluid and electrolyte absorption has been described in a rat model of acetic acid-induced colitis, although the small intestinal histology remained normal with no evidence of any inflammatory reaction.^{29,30} In addition, up to 50% decrease in jejunal fluid absorption was observed in iodoacetamide-induced colitis.³¹ A decrease in the absorption of alanine¹⁷ and glucose³² was also demonstrated in iodoacetamide and trinitrobenzene sulphonic acid [TNBS]-induced colitis as well as in a novel model of colitis induced by localized electrolytic colonic lesion^{33,34} [Table 2]. These changes may occur immediately after ulcer induction, and jejunal function returns to normal following ulcer healing.

2.2. Permeability changes

Several studies have found that colitis may be associated with increased permeability in distant small intestinal sites, reflecting abnormalities in intestinal function or structure. Most of these studies were performed in animal models.^{29,35,36} Cui *et al.*²⁹ described an increase in ileal permeability in acetic acid-induced colitis, and Fries *et al.*³⁵ reported a 70% increase in intestinal permeability in TNBS-induced colitis associated with an alteration in the transmembrane protein occludin [Table 2]. Recent human studies have confirmed increased small intestinal permeability in subsets of patients with UC even in the absence of inflammation.²⁰ This change in permeability may have an effect on water and nutrient absorption, may explain the increased prevalence of irritable bowel syndrome²² and food allergy³⁷ in IBD and may play a role in the natural history of the disease. It is now well established that both cytokines and the enteric nervous system interfere with the normal role of the epithelial cells in the regulation of barrier function, by inducing changes in the function and structure of tight junctions.^{38,39} Therefore, this permeability disturbance may be explained by the increase in cytokines production in distant small intestinal sites and the changes in the enteric nervous system in colitis.

Table 1. Clinical reports on the effect of ulcerative colitis on small intestinal absorption.

Number of patients	Measurement	Results	Reference
<i>n</i> = 3	Jejunal perfusion	↓ amino acids absorption	Zetzel, <i>et al.</i> ²⁵
<i>n</i> = 4	Jejunal perfusion	↓ water & electrolytes absorption	Binder, <i>et al.</i> ¹⁴
<i>n</i> = 60	D-Xylose	Abnormal in 6 out of 30 patients	Salem, <i>et al.</i> ¹⁶
	Faecal fat	↑ in 18 patients	
<i>n</i> = 22	D-Xylose	Abnormal in 8 out of 18 patients	Chakravarti, <i>et al.</i> ¹³
	Faecal fat	Mild steatorrhoea in 7 out of 22 patients	
<i>n</i> = 25	D-Xylose	Abnormal	Andersson, <i>et al.</i> ¹⁵
	Serum folic acid	↓	
	Faecal fat	> 6 g/24h in 50% of patients > 10 g/24h in 25% of patients	
<i>n</i> = 23	D-Xylose	Normal	Soule, <i>et al.</i> ¹⁹
	Serum folic acid	↓	
	Folic acid absorption	↓	
<i>n</i> = 7	D-Xylose	Normal	Rao, <i>et al.</i> ⁴⁹
	Faecal fat	Normal	

↑, ↓, increase and decrease, respectively. Similar symbols will be used in the next tables.

Table 2. Effect of experimental colitis on small intestinal absorption, permeability and brush border enzymes activity and expression.

Animal model	Measurement	Results	Reference
Acetic acid	Fluid absorption <i>in vivo</i>	↓ Ileal absorption No change in jejunal absorption	Empey, <i>et al.</i> ³⁰
Acetic acid	Fluid and electrolytes absorption <i>in vitro</i> Permeability <i>in vitro</i>	↓ Ileal absorption ↑ Ileal permeability	Cui, <i>et al.</i> ²⁹
Iodoacetamide	Alanine absorption <i>in vivo</i>	↓ Jejunal absorption	Barada, <i>et al.</i> ¹⁷
Iodoacetamide	Fluid absorption <i>in vivo</i>	↓ Jejunal absorption	Mourad, <i>et al.</i> ³¹
Electrocautery	Fluid absorption <i>in vivo</i>	↓ Jejunal absorption	Mourad, <i>et al.</i> ³⁴ Barada, <i>et al.</i> ³³
Iodoacetamide	Glucose absorption <i>in vivo</i>	↓ Jejunal absorption	Mourad, <i>et al.</i> ³²
TNBS	Permeability	↑ in all small intestine	Fries, <i>et al.</i> ³⁵
TNBS	Permeability	<i>In vivo</i> : ↑ to EDTA	Pantzar, <i>et al.</i> ³⁶
Ethanol	Permeability	<i>In vitro</i> : ↑ to ovalbumin in distal small intestine	
Oxazolone			
TNBS	Brush border enzymes	↓ activity and expression	Amit-Romach, <i>et al.</i> ⁶⁵
Iodoacetamide	Brush border enzymes GLUT 5	↓ activity and expression ↓ expression	Jurjus, <i>et al.</i> ⁶⁶

TNBS, trinitrobenzene sulphonic acid.

2.3. Motility derangement

It is well established that inflammation may affect the motor function of the large bowel as evidenced by *in vivo*^{40–44} and *in vitro*⁴⁵ studies. The dysmotility may be due to inflammatory mediators and changes in neural circuitry. Such changes may persist even after the inflammation has subsided.^{46,47} However, only a few studies have investigated small intestinal motor function in patients with ulcerative colitis, as the manometric techniques used to study intestinal motility are quite invasive, necessitating deep intestinal intubation for a prolonged period of time. Small intestinal transit time has been found to be reduced in patients with colitis, secondary to decreased intraluminal pressures and a lower rate of intestinal propulsion irrespective of severity of inflammation or remission.^{48–50} In addition, Rao *et al.*⁴⁹ found that the mouth-to-acecum transit was significantly slower in 62 patients with UC as compared with healthy volunteers although there was no change in gastric emptying, pointing to a small intestinal motility dysfunction. Recently, an increased oro-caecal transit time [OCTT] in patients with UC was found to be associated with small intestinal bacterial overgrowth [SIBO].⁵¹ An increase in plasma levels of circulating cytokines correlated with a prolonged OCTT and an increased prevalence of SIBO. Finally, some studies have shown significant small intestinal distention and increase in gas associated with severe colitis, findings that may predict poor response to treatment and development of toxic megacolon.^{12,52,53}

Abnormalities of the colonic microbiota [or dysbiosis] have been well documented in patients with UC.^{54–56} This alteration may lead to enhanced autoimmune attack against gut cells, increased permeability and altered cytokines production. Whether similar changes occur in the small intestine, resulting in intestinal dysfunction, is not known.

Induction of colitis in rats reduced gastrointestinal propulsion of a charcoal suspension *in vivo*.⁵⁷ In addition, Aube *et al.*⁵⁸ found that colitis was associated with increased frequency of migrating motor complexes in the non-inflamed ileum, characterized mainly by a decrease in the duration of phases I and III, whereas the occurrence of ileal giant migrating complexes remained unchanged. Although the underlying mechanism remains undetermined, it has been shown

that this was not mediated by nitric oxide, prostaglandins or muscarinic acetylcholine receptors.⁵⁸ Finally, increased excitability of ileal after-hyperpolarization [AH]-neurons was reported to occur during and after recovery from TNBS colitis, despite absence of ileal inflammation. These changes did not correlate with changes in ileal motility.⁵⁹

3. Small intestinal structural and biochemical alterations in colitis

Changes in small intestinal histology have been described in patients with colitis as well as in experimental animal models. Partial villous atrophy, abnormal crypt/villus ratio and other morphological alterations^{13,16,19,60,61} have been described in UC patients. These changes may disappear during remission.¹³ The prevalence of these changes is variable in the different reports, ranging between 5% and 71%. In addition, Ferguson *et al.*⁶² showed an increase in lamina propria plasma cells, but not lymphocytes or eosinophils, in the jejunum of patients with ulcerative colitis [Table 3]. These changes were not affected by the activity of the colitis, by its extent or by the intake of steroids. An association between coeliac disease and IBD has been previously suggested although recent studies did not show an increased prevalence of coeliac disease in UC patients.^{63,64} Thus, it is unlikely that small bowel dysfunction seen in UC is due to associated coeliac disease. Findings in animal models are also controversial, with some studies showing morphological alterations in the small intestine of animals with experimental colitis, such as smaller villous surface area in jejunum and ileum,⁶⁵ whereas others found minimal⁶⁶ or no pathological changes despite the functional abnormalities.^{17,29,31,33,34,58,67,68}

On the other hand, biochemical abnormalities found in patients with UC include a decrease in the expression of some small intestinal enzymes such as sucrase, lactase and trehalase^{60,69–75} [Table 3]. The impact of these changes on the clinical status of dehydration and malnutrition seen in patients with IBD is not known. In addition, the pathophysiology and the role of the colonic inflammation and the inflammatory mediators in these changes are far from understood.

Table 3. Clinical reports on the effect of ulcerative colitis on small intestinal histology and brush border enzymes activity.

Number of patients	Findings	Reference
<i>n</i> = 60	Partial villous atrophy during severe UC	Salem, <i>et al.</i> ¹⁶
	Normal epithelial cells & Microvilli on electron microscope	
<i>n</i> = 10	Partial villous atrophy in 4 patients	Jankey, <i>et al.</i> ⁶¹
<i>n</i> = 22	Morphological changes in 6 patients	Chakravarti, <i>et al.</i> ¹³
<i>n</i> = 31	Abnormal in 71% of patients: mild abnormalities of villus architecture to marked reduction of villous height	Arvanitakis, <i>et al.</i> ⁶⁰
<i>n</i> = 23	Abnormal in in 5% of patients: changes in crypt/villous ratio	Soule, <i>et al.</i> ¹⁹
<i>n</i> = 20	Increase lamina propria plasma cells	Ferguson, <i>et al.</i> ⁶²
<i>n</i> = 1	Normal mucosa	Struthers, <i>et al.</i> ⁷²
<i>n</i> = 14	Normal mucosa	Dunne, <i>et al.</i> ⁷⁵
<i>n</i> = 31	↓ activity of lactase, sucrase, trehalase, Dipeptidases	Arvanitakis, <i>et al.</i> ⁶⁰
<i>n</i> = 32	lactase deficiency in 46% of patients	Cady, <i>et al.</i> ⁷³
<i>n</i> = 3	↓ activity of lactase in 1 patient	Frazer, <i>et al.</i> ⁶⁹
<i>n</i> = 4	↓ activity of lactase in 1 patient	Sheehy, <i>et al.</i> ⁷¹
<i>n</i> = 1	↓ activity of lactase	Struthers, <i>et al.</i> ⁷²
<i>n</i> = 12	↓ activity of lactase during acute exacerbation	Gudmand-Hoyer, <i>et al.</i> ⁷⁰
<i>n</i> = 14	No change in enzymes activity	Dunne, <i>et al.</i> ⁷⁵
	No change in enzymes activity	d'Inca, <i>et al.</i> ⁷⁴

Again, animal studies have reproduced the findings in humans and described a decrease in jejunal lactase, sucrase, aminopeptidase and brush border GLUT-5 expression which occurred a few days after induction of colitis⁶⁶ [Table 2]. These enzymes returned to normal following the disappearance of the inflammation, except for sucrase and crypt GLUT-5 expression.⁶⁶ Similarly, Amit-Romach *et al.*⁶⁵ showed a decreased expression and activity of sucrase-isomaltase in the ileum of rats with TNBS-induced colitis, whereas aminopeptidase activity was lower in the jejunum. They showed also a decrease in jejunal and ileal relative amounts of gel-forming mucin [MUC2] mRNA secreted by goblet cells and an increase in the membrane-bound mucin [MUC3] mRNA secreted by enterocytes, implying a differential effect of colitis on the small intestine.

4. How can these changes be explained?

The cross-talk between the colon and the small intestines and the resulting functional and structural disorders may be attributed to alterations in the neural circuitry, secreted cytokines or other neurohumoral mediators.

4.1. Role of the gastrointestinal innervation

The enteric nervous system [ENS] constitutes an extensive network linking all parts of the gastrointestinal [GI] tract on one hand, and regulating all exchanges with internal and external environments on the other. In addition, all components of the GI tract, including the ENS, muscle layers, glands, epithelial cells, blood vessels and immune cells are connected to the central nervous system [CNS] through afferent and efferent nerve fibers, known as extrinsic innervations. The ENS regulates, in concert with the CNS, all GI functions [including motility, absorption, secretion, blood circulation and possibly immune reactions] through enteric reflexes that can be triggered by the activation of the intrinsic primary afferent neurons [IPAN] and propagated through a complex circuitry of interneurons, motor neurons, short and long association neurons, and intestinofugal neurons [Figure 1]. All intrinsic regulations of gut functions can be also initiated and/or modulated by the CNS through the extrinsic afferent and efferent innervations. This afferent system can be at the origin of activation of several efferent loops, including the sympathetic and parasympathetic systems and neuroimmune loops, such

as the hypothalamo-pituitary-adrenal axis [HPA]. This complex and apparently redundant neural wiring can explain the behaviour of the GI tract throughout its extent, as a single entity during normal and pathological conditions.

Early clinical observations pointed out the fact that spreading of the effect of colitis to other inflamed and non-inflamed areas might involve the GI innervation that can play a dual role as a modulator or as a target of inflammation [Figure 2].^{7,76-78}

Data from clinical and experimental studies on the impairment of the bowel innervation, due to IBD, revealed several facts observed in intestinal segments not involved in inflammation. These include derangement of the function of GI sensory and motor neurons,^{7,44,78} such as prolonged hyperexcitability,⁷⁷ increased reflexes due to hyperactivation of IPAN and extrinsic afferent neurons [Figure 2],⁷⁹ significant changes in the expression and release of neuropeptides substance P [SP] and somatostatin,^{80,81} and adrenergic, cholinergic and serotonergic neurotransmitters or their receptors.^{57,82} In addition, discrete structural changes have been described that include neuronal loss^{83,84} or neuronal degeneration followed by abnormal sprouting of the remaining nerve fibres.⁸⁵

On the other hand, several recent studies emphasized the modulatory role of the GI innervation in bowel inflammation. This role can take the aspect of a contribution to the spreading of inflammation through one or more of the following mechanisms: an alteration of cholinergic and adrenergic neurotransmission through increased expression of prejunctional α 2-adrenoceptors⁵⁷; an increase in SP and the vanilloid receptor TRPV1, and a reduction in somatostatin immunoreactive nerve fibres⁸⁰; increased release of the neuropeptides calcitonin gene-related peptide [CGRP] and SP, which can induce neurogenic inflammation⁸¹; and abnormal function of the extrinsic innervation illustrated by a recovery or attenuation of bowel inflammatory syndromes following selective block or ablation of CSPA fibres.^{81,86} This role, however, has been challenged by other studies showing a protective function of GI innervation in various experimental models of bowel inflammation.^{17,82,87}

It has already been demonstrated that the ENS plays an important role in regulating intestinal fluid,^{88,89} alanine⁹⁰ and glucose absorption.⁹¹ Early observation on the decrease of jejunal nutrient absorption in an animal model of colitis reported a more severe decrease in rats subjected to ablation of their CSPA fibres¹⁷; this decrease, however,

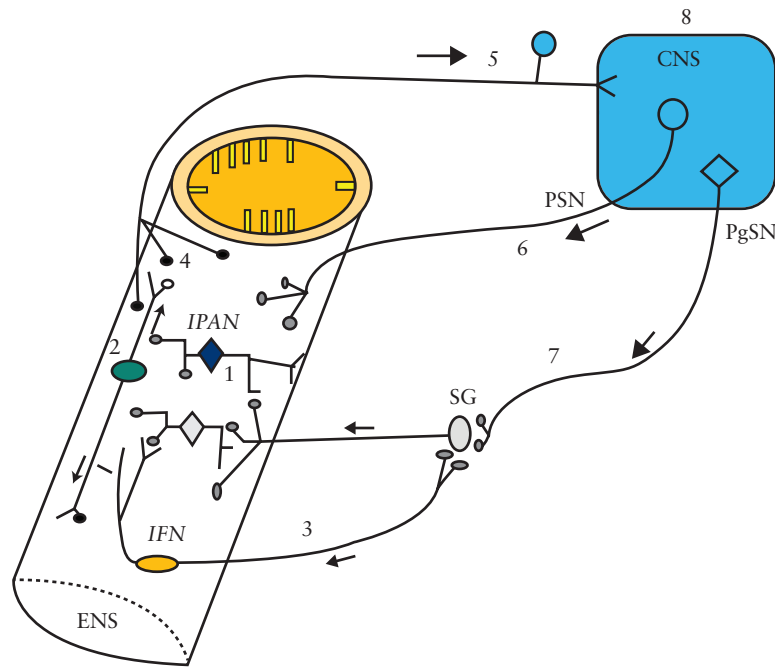


Figure 1. Simplified diagram showing the basic neuronal and neurohumoral loops involved in gastrointestinal homeostatic regulations. The numbers are used to label the basic wiring of the loops: 1: local sensory [epithelial]-motor loop; 2: intersegmental ascending and/or descending loop; 3: intestinofugal-sympathetic loop; 4: local effector loop based on secretion of neuropeptides by the peripheral terminals of capsaicin-sensitive primary afferents fibers; 5: extrinsic afferent loop [spinal and vagal afferent fibers]; 6: parasympathetic efferent loop; 7: sympathetic loop; 8: hypothalamo-pituitary-adrenal axis. The arrows indicate the direction of nerve impulses. CNS, central nervous system; ENS, enteric nervous system, IFN, intestinofugal neuron; IPAN, intestinal primary afferent neuron; PgSN, preganglionic sympathetic neuron; PSN, parasympathetic neuron; SG, sympathetic ganglion.

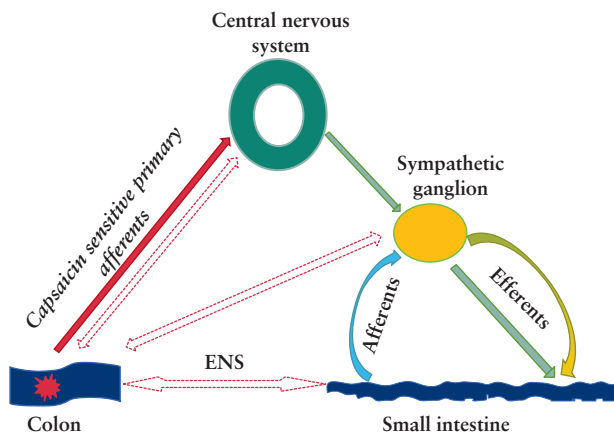


Figure 2. Schematic representation of the neural pathways involved in the spreading of the effects of colitis. One-headed arrows represent the direction of the effects and double-headed arrows represent paths for reciprocal interactions. Filled arrows indicate established pathways and empty arrows represent reciprocal neuroimmune interactions based on functional evidence. Note the multiplicity of the reverberating loops that may explain the long-lasting and remote effects of a discrete colonic injury or inflammation.

was not affected by sub-diaphragmatic vagotomy. In addition, both tetrodotoxin [TTX] and benzylalkonium chloride [BAC] treatments resulted in a complete reversal of the effect of colitis on jejunal fluid absorption in a rat model of colitis,³¹ implying that an intact myenteric plexus is needed for the remote intestinal changes observed in colitis. Furthermore, involvement of the extrinsic innervations in the decrease of intestinal glucose absorption in colitis was recently demonstrated.³² Blandizzi *et al.*⁵⁷ presented convincing evidence that experimental

colitis in rats leads to distinct changes in the neural circuitry of non-inflamed regions of the bowel, which may explain the changes in small bowel motility that accompany colitis. Further support came from more recent studies demonstrating the protective effect of both afferent and efferent components of the extrinsic GI innervation against colonic injury. The vanilloid receptors TRPV1, located on the CSPA fibres, have been shown to mediate the endogenous protecting mechanisms against induced colonic ulcer.^{92,93} The protective effect of the extrinsic afferents is further enhanced by the anti-inflammatory role played by the parasympathetic efferents to the GI tract. As illustration, vagal stimulation has been shown to alter the role of immune cells through the release of acetylcholine and the activation of nicotinic cholinergic receptors, which can modulate immune reactivity of macrophages and reduce their cytokine secretion.^{82,87}

4.2. Role of cytokines and neurohumoral mediators

In addition to the observed basal low level of inflammation in the GI tract under normal conditions,⁹⁴ several studies reported a basal expression of low level of tumour necrosis factor alpha [TNF- α], interleukin 1 beta [IL-1 β], and interleukin 6 [IL-6] and its increase in human IBD and experimental colitis. This increase was observed in the inflamed mucosa of the colon^{3,95-97} and may correlate with the severity of inflammation.^{95,96,98} Furthermore, several studies reported significant upregulation of pro-inflammatory cytokines in macroscopically and microscopically unaffected intestinal areas of patients with UC and CD.⁹⁹⁻¹⁰¹ In addition in rat models of acute and chronic colitis, increased levels of pro-inflammatory cytokines TNF- α , IL-1 β and IL-6 were demonstrated in distant segments of the small intestine without any significant histological changes.^{33,34,67} These studies revealed that this increase was not restricted to pro-inflammatory cytokines [TNF- α , IL-1 β and IL-6] but involved also an

upregulation of anti-inflammatory cytokines and mediators, such as IL-10 and nerve growth factor [NGF].¹⁰² Both observations suggest a remote effect of colonic inflammation and its own auto-regulatory mechanisms.¹⁰² The question of how an inflammation or an ulcer in the colon may induce upregulation of cytokines in a distant site remains unanswered. Are these cytokines produced in the colon and then transported to the different parts of the small intestine by blood stream [circulating cytokines] or are they secreted locally by the non-immune cells and/or residing immune cells through a neural or neurohumoral reflexes?

To answer this question, we have recently demonstrated an increase in *de novo* mRNA expression of these cytokines in remote intestinal areas in TNBS and iodoacetamide-induced colitis¹⁰³ as well as in electrocautery-induced colitis.^{33,34} These findings and those of others suggest that several types of small intestinal cells in unaffected segments can secrete both pro-inflammatory and anti-inflammatory cytokines in colitis.^{99,104} Furthermore, other studies have shown that the acute inflammatory response of TNBS can alter neural function in the myenteric plexus at both inflamed and non-inflamed sites in the intestine^{105,106} and that exogenous application of IL-1 β in control tissue can mimic this alteration in neural function.¹⁰⁷ In addition cytokines present in the inflamed intestine, such as IL-1 and IL-3, can directly affect neural function by altering neurotransmitter release and acutely affecting the ENS,¹⁰⁸ or by inducing neuronal death followed by abnormal sprouting of the axons of the remaining neurons.⁸⁵ Therefore, cytokines can act at non-inflamed sites to alter intestinal function through neural and non-neural mechanisms.¹⁰⁹ Various findings suggest that inflammatory mediators may play a role in malabsorption and other small intestinal malfunctions associated with colitis. For example, cytokines have been shown to alter the transport of water, sodium, chloride, glucose and amino acids in the gut.^{110–114} TNF- α has a 40% inhibitory effect on L-leucine uptake in rabbit jejunum, probably through its effect on fluid and chloride secretion.¹¹⁵ In addition, it has been shown that TNF- α inhibits D-fructose and D-galactose intestinal transport in rabbits and decreases the number of GLUT-5 and SGLT-1 transporters at the brush border membrane.^{116–118} Moreover, IL-1 β inhibits rat jejunal galactose absorption,¹¹⁸ most likely through inhibition of sodium potassium ATPase, which may affect all sodium-dependent nutrient transport.¹¹⁴ On the other hand, cytokines may also change the motility of the small intestine and colon of experimental animals, which can contribute to diarrhoea.^{40,119–122} Therefore, cytokines can modify the function of the enteric nervous system, which in turn might alter ion and nutrient transport and motility.^{123–126}

Several neurohumoral mediators, including vasoactive intestinal polypeptide [VIP], nitric oxide [NO], 5-hydroxytryptamine [5-HT] and substance P, have been found to be increased in the inflamed mucosa and are known to affect water and nutrient absorption.⁸⁸ Do these mediators play any role in the small bowel dysfunction in colitis?

VIP is a neurotransmitter found in the myenteric plexus, lamina propria and mucosa of the small and large intestine. It is a potent stimulant of mucosal water and electrolyte secretion, it is involved in the peristaltic reflex and plays an inhibitory role on immune cell function.¹²⁷ Some studies have shown an increase in VIP levels and its mRNA expression as well as increased VIPergic neurons in the colon of patients with ulcerative colitis as compared with controls.^{128–130} Similarly, plasma VIP levels have been found to be elevated in UC patients.¹³¹ Yet no studies have looked at VIP levels in the small intestine of patients with colitis or in experimental colitis. Studies from our laboratory demonstrated that VIP plays an important role in causing a decrease in jejunal fluid absorption in chemical colitis, as this decrease was completely inhibited by the VIP antagonist [4Cl-D-Phe,⁶Leu¹⁷]VIP.³¹

Nitric oxide [NO] production has also been found to be increased in IBD and experimental colitis,^{132,133} but whether it plays a role in its pathogenesis or in the associated diarrhoea has not been elucidated. The effect of NO on intestinal fluid transport has been subject of controversial reports, with many studies showing a pro-absorptive effect and other studies proving a pro-secretory effect.^{134,135} It has been found that administration of the NO synthase inhibitor L-NAME and the neural NOS inhibitor L-NI resulted in a significant inhibition of the effect of colitis on small intestinal fluid absorption. This may imply that the decrease in intestinal fluid absorption in colitis could be through either an increase in NO-containing neurons or to a reflex stimulation of these neurons induced by colonic inflammation and release of cytokines.³¹

Serotonin [5-HT] has been found to be increased in the colon of patients with chronic ulcerative colitis^{136,137} and in the inflamed mucosa of rats and guinea pigs with experimental colitis.^{138,139} Although 5-HT is a known potent intestinal secretagogue and was found to be increased in non-inflamed segments of jejunum and ileum in TNBS colitis,¹³⁹ it seems that it does not play a role in the decrease in jejunal fluid absorption in colitic rats, as the 5-HT₃ receptor antagonist granisetron and the 5-HT₃ and 5-HT₄ receptor antagonist tropisetron did not prevent this decrease.³¹

5. Conclusion

Ulcerative colitis is associated with significant alterations in the function of the small intestine as manifested by a decrease in the absorption of fluid and nutrients and an increase in permeability. Complex neuro-immune mechanisms have been shown to play an important role in these changes. Functional and structural alterations of the gut innervation can affect distant intestinal areas and stimulate immune mechanisms that can contribute to spreading the inflammation to various parts of the GI tract [Figure 2]. The resulting increase in the level of pro-inflammatory mediators, including cytokines, can affect intestinal function and potentiate further neuronal dysfunction. Thus, this discrete cross-talk between different parts of the GI tract can be mediated through an immunogenic and neurogenic vicious cycle of inflammation observed in colitis [Figure 2].

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Author Contributions

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