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Review article: the role of butyrate on colonic function

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Summary

Background Butyrate, a short-chain fatty acid, is a main end-product of intestinal microbial fermentation of mainly dietary fibre. Butyrate is an important energy source for intestinal epithelial cells and plays a role in the maintenance of colonic homeostasis.

Aim To provide an overview on the present knowledge of the bioactivity of butyrate, emphasizing effects and possible mechanisms of action in relation to human colonic function.

Methods A PubMed search was performed to select relevant publications using the search terms: 'butyrate, short-chain fatty acid, fibre, colon, inflammation, carcinogenesis, barrier, oxidative stress, permeability and satiety'.

Results Butyrate exerts potent effects on a variety of colonic mucosal functions such as inhibition of inflammation and carcinogenesis, reinforcing various components of the colonic defence barrier and decreasing oxidative stress. In addition, butyrate may promote satiety. Two important mechanisms include the inhibition of nuclear factor kappa B activation and histone deacetylation. However, the observed effects of butyrate largely depend on concentrations and models used and human data are still limited.

Conclusion Although most studies point towards beneficial effects of butyrate, more human *in vivo* studies are needed to contribute to our current understanding of butyrate-mediated effects on colonic function in health and disease.

Introduction

Short-chain fatty acids (SCFAs), primarily acetate, propionate and butyrate, are organic acids produced within the intestinal lumen by bacterial fermentation of mainly undigested dietary carbohydrates, but also in a minor part by dietary and endogenous proteins, such as mucous, and sloughed epithelial cells.[1] Most micro-organisms prefer to ferment carbohydrate over protein and therefore saccharolytic bacterial fermentation occurs predominantly in the proximal colon, while proteolytic fermentation mainly takes place in the distal colon where fermentable carbohydrates are depleted. The latter is considered less favourable for the host because potentially toxic metabolites are formed such as ammonia, sulphur-containing compounds, indoles and phenols. As this distal part of the colon is the predominant location of several gastrointestinal disorders, such as ulcerative colitis (UC) and colon cancer, it could be hypothesized that the production of these toxic metabolites and a lower availability of SCFAs are involved in the pathogeneses of these diseases.[2, 3]

The production of SCFAs allows the salvage of energy mainly from carbon sources as dietary fibre that is not digested in the small intestine. It has been estimated that SCFAs can contribute to about 5–15% of the total caloric requirements of humans.[4] An important SCFA produced is butyrate that besides being an energy source for the epithelial cells also influences a wide array of cellular functions affecting colonic health. As such, butyrate may have an anticarcinogenic and anti-inflammatory potential, affect the intestinal barrier and play a role in satiety and oxidative stress.

Because of this important role of butyrate and the rather low consumption of fermentable dietary fibre in today's Western diet, food manufacturers are interested in adding fibre sources to foods and beverages that rely on slow bacterial fermentation to increase distal colonic butyrate concentrations. In medical application, butyrate has also been proposed as a potential therapeutic agent for colonic inflammation.[5] In a book by Cummings *et al.* published in 1995,[6] the effects of butyrate have been nicely reviewed, but the reported effects have often been based on *in vitro* and animal data. During the last decade, additional human (intervention) studies were published and knowledge on possible mechanisms of action is improving. This review summarizes the present knowledge on the bioactivity of butyrate, emphasizing effects and possible mechanisms of action in relation to human colonic function (Figure 1).

Figure 1

Open in figure viewer | PowerPoint

Different domains that may be affected by bulyrate produced in the colonic lumen.

Production and absorption of SCFAs

Total and relative molar concentrations of the main SCFAs, acetate, propionate and butyrate produced in the human intestine, depend on the site of fermentation, diet and composition of the intestinal microbiota.[7] Absolute concentrations of butyrate in human faeces were found to range from 11 to 25 mM,[8, 9] and molar ratios of acetate to propionate to butyrate varied between 48:29:23 and 70:15:15, respectively, with mean values of approximately 60:20:20.[1, 9] However, the *in situ* production of total colonic SCFAs is difficult to determine because more than 95% of the SCFAs are rapidly absorbed and metabolized by the host.[1] Subsequently, faecal concentrations of SCFAs are not necessarily representative of those in the more proximal colon and can also be affected by intestinal transit time.[10] Probably for these reasons, various studies were not able to show effects of different fermentable substrates on faecal SCFA concentrations.[11, 12]

Because of the difficult accessibility of the human colon, estimates of luminal SCFA concentrations are based on analyses in human gut contents of sudden-death victims[13, 14] and stomal effluent of patients with transverse or sigmoid colostomy.[15] In autopsy samples, total SCFA concentrations varied from 137 to 197 mmol/kg chyme in the caecum to 86 to 97 mmol/kg chyme in the descending colon.[13, 14] In transverse colostomy samples SCFA concentrations were high (1400 mol/kg dry matter) compared to those in sigmoid colostomy samples (550 mol/kg dry matter), which were similar to the concentrations in faeces from controls.[15] In line with the SCFA concentrations, the pH value is the lowest in the proximal colon (pH ≈ 5.6) and increases towards the distal colon (pH ≈ 6.3).[14]

As SCFAs are weak acids (p*K*a ≈ 4.8), more than 90% exist in the anionic, dissociated form in the colonic lumen.[16] Several different mechanisms of uptake of SCFAs across the apical membrane of the colonocytes have been proposed, including diffusion of the undissociated (lipid soluble) form,[16] SCFA/HCO_3^- exchange[17, 18] and active transport of the dissociated form by SCFA-transporters. Two SCFA-transporters have been reported: the monocarboxylate transporter isoform 1 (MCT1), which is coupled to a transmembrane H^+-gradient[19] and SLC5A8, which is a Na^+-coupled co-transporter and is also denoted sodium-coupled monocarboxylate transporter (SMCT1).[20] SCFAs, with butyrate being the most potent one, hereby stimulate the

absorption of sodium and water[21] and can be considered as antidiarrhoeal agents.[22] The transport mechanisms involved in basolateral transport of SCFAs are still unclear.

The majority of the absorbed butyrate is metabolized by the colonic epithelium, resulting in low concentrations of butyrate in portal blood. Human portal butyrate concentrations ranged from 1.3 to 14.4 μM in patients during gall-bladder surgery[23] and from 14 to 64 μM in sudden death victims.[14] Most likely, the liver subsequently extracts the majority of the remaining butyrate, resulting in even lower venous systemic serum butyrate concentrations ranging from 0.5 to 3.3 μM.[24-27] Serum concentrations of propionate and acetate in peripheral blood have been shown to range from 3.8 to 5.4 and from 98 to 143 μM, respectively.[24-27]

Delivery of butyrate

An important source of butyrate is colonic fermentation of dietary fibre. The rate and amount of butyrate being produced along the colonic lumen during dietary fibre supplementation depends on its chemical structure, such as solubility and degree of polymerization. Insoluble fibres (e.g. cellulose and lignin) have a rather low fermentability, but are associated with increased faecal mass and decreased colonic transit time. Soluble fibres are highly fermentable and hence generate greater quantities of SCFAs in the colon.[28] Fibres with a higher degree of polymerization are more resistant to saccharolytic fermentation resulting in prolonged fermentation, expanding towards the distal colon.[29] Examples of fermentable dietary and chemically modified fibres that are associated with a higher production of SCFAs either *in vitro* or *in vivo* are oligofructose,[30] inulin,[31] psyllium,[32] germinated barley foodstuff,[33] hydrolysed guar gum,[34] oat bran,[9, 35] corn starch,[12] isomalt,[11] gluconic acid[36] and butyrylated starch.[37] Although the beneficial effects of these fibres are often attributed to the increased butyrate production, these soluble fibres can also affect other intestinal characteristics influencing intestinal health, such as increased faecal bulk, shortened colonic transit time, changes in the composition of the gut microbiota, lowered intraluminal pH and changed bile acid profiles.[38]

Apart from dietary fibres, also other ingested substrates can contribute to an increase in the colonic butyrate concentrations by different mechanisms. An example is the oligosaccharide acarbose that increases the amount of starch entering the colon by acting as an α-glucosidase inhibitor.[8, 25] In addition, tributyrin, a triglyceride containing three butyrate molecules esterified to glycerol, augments butyrate concentrations after hydrolysation by pancreatic and gastric lipases.[39] Also, butyrate tablets coated with a slow release pH-dependent coating releasing butyrate in the distal ileum and proximal colon can be used.[40, 41] However, these tablets may not always disintegrate and release their content at the intended location because of interindividual differences in intracolonic pH and transit time.[42] Finally, consumption of several types of butyrate-producing probiotic bacterial strains, such as *Butyrivibrio fibrisolvens*[43] and *Clostridium butyricum*,[33, 44] has been studied in animal models.

Besides using oral substrates to increase colonic butyrate concentrations, a number of clinical intervention studies in patients with distal colonic inflammation have applied rectal enemas to deliver butyrate to the distal colon.[45] However, use of enemas is often hampered by a low compliance rate and a short and discontinuous exposure of the colon mucosa to butyrate.[46] These studies will be discussed in a later section.

Butyrate and colon carcinogenesis

One of the proposed beneficial effects of butyrate on human intestinal health is the prevention and inhibition of colon carcinogenesis. Although epidemiological studies are still inconclusive, most of these studies showed an inverse relationship between dietary fibre intake and the incidence of colorectal cancer.[40, 41, 47-53] Several studies hypothesized that increased colonic concentrations of butyrate are an important mediator in the observed protective effect of fermentable dietary fibre.[32, 47, 54, 55] In many of these studies, however, the physiological properties of the ingested dietary fibres have not been considered.[56] A role for butyrate in the development of colon cancer has recently been supported by the downregulation of butyrate transporters (MCT1 and SMCT1) in human colon cancer tissue,[57, 58] which results in a reduced uptake and metabolism of butyrate in the colonocytes. In addition, the SMTC1 activity was positively correlated with the disease-free survival.[59] Moreover, a lower butyrate to acetate ratio has been found in luminal samples of patients with adenomatous polyps or colon cancer vs. healthy controls.[60] Although several well-designed animal models have demonstrated a protective effect of butyrate on colorectal carcinogenesis,[55, 61-67] direct evidence for a protective effect of butyrate on carcinogenesis in humans is still lacking.

Knowledge and hypotheses concerning the mechanistic effects of butyrate on carcinogenesis are mainly based on *in vitro* cell systems. *In vitro* exposure of many tumour cell lines to butyrate leads to anticarcinogenic effects by induction of apoptosis,[68, 69] inhibition of proliferation[70, 71] and promotion of a more differentiated phenotype.[70, 71]

In contrast to these relatively consistent findings in tumour cell lines, the observed effects of butyrate on noncarcinogenic cells are more diverse and do not always point in the same direction as in tumour cells.[70, 72] Also, some data from human (intervention) studies are available, which focus predominantly on the effect of SCFAs on colonocytic proliferation. Treatment with SCFA enemas for 2 weeks increased rectal proliferative activity in patients with a closed atrophic rectum that was deprived of its natural SCFA source.[73] In a study by Scheppach *et al.,*[74] human colonic biopsies were exposed to butyrate *ex vivo* for 4 h, which revealed that butyrate increased the proliferation rate at the basal 60% area of the crypt. It has been proposed that butyrate stimulates the physiological pattern of proliferation that is normally confined to the basal crypt.[75] Expansion of the proliferative zone towards the crypt surface has been considered a biomarker of increased susceptibility to cancer formation.[76] In

colonic biopsies from patients with UC, expansion of the proliferative zone has been shown and has been found to be independent of the degree of inflammation.[77] Treatment with butyrate enemas for 2 weeks decreased the proliferation rate in the upper part of the crypt in colonic biopsies of active UC patients, resulting in values comparable to those of healthy control subjects.[45]

These apparent contradicting effects of butyrate found in normal colonocytes and in neoplastic cells are often referred to as the 'butyrate paradox'.[70] There are several explanations for these contrasting effects. First, they may reflect the inherent differences of the cells, the cells' state of activation and their energy status. Furthermore, it may be the result of different concentrations of butyrate and the different exposure times to butyrate used in these experiments. Finally, the ability of the cells to β-oxidize butyrate may influence their response to butyrate, as it can influence the rate of removal of butyrate from the cytoplasm and hence the availability of butyrate to exert its effects.[78], [79]

Mechanisms of butyrate's anticarcinogenic effect

Although the exact underlying mechanisms of action have not yet been elucidated, the ability of butyrate to influence cell function is considered to be because of its regulation of gene expression, which is often attributed to its inhibition of histone deacetylase (HDAC).[78], [80] This results in hyperacetylation of histones and enhancement of the accessibility of transcription factors to nucleosomal DNA.[69], [81], [82] However, it is likely that butyrate has other intracellular targets, including hyperacetylation of nonhistone proteins, alteration of DNA methylation, selective inhibition of histone phosphorylation and modulation of intracellular kinase signalling.[80] This multiplicity of effects may underlie the ability of butyrate to modulate gene expression and have impact on key regulators of apoptosis and cell cycle as was demonstrated for cell cycle inhibitor p21[69], [81] and proapoptotic protein BAK.[68], [83] Interestingly, cancer cells appear to be more sensitive to the actions of HDAC inhibitors than nontransformed cells, but the mechanistic basis for this apparent selectivity is poorly understood.[83]

One of the effects also demonstrated in humans is the effect of butyrate on the plasminogen/plasmin system (PPS). Increases in tumour and serum levels of several components of the PPS are found to correlate with a more invasive tumour cell phenotype and a worse prognosis in patients with colon cancer.[84] *In vitro*[85] and *in vivo* studies[86], [87] have shown that butyrate is able to alter the balance of components of the PPS in a manner that favours net decreased plasminogen activator activity.

Other effects of butyrate studied in multiple colonic cancer cell lines include the enhancement of the activity of the detoxifying enzyme glutathione-*S*-transferase.[88] Furthermore, butyrate may have an inhibitory effect on tumour cell migration by inhibiting decay-accelerating factor (DAF) expression[89] and pro-metastatic metalloproteinase activation.[90], [91] Finally, it has also

been suggested that butyrate inhibits tumour-induced angiogenesis through modulation of two angiogenesis-related proteins, vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF)-1α.[92]

In conclusion, butyrate may have a protective role in the prevention and progression of colorectal carcinogenesis. However, the effects on apoptosis and proliferation appear to differ between normal and neoplastic tissue. The different models and concentrations being used may partly explain this paradox. Therefore, effects and mechanisms identified by *in vitro* models have to be confirmed in humans under physiological conditions.

Butyrate and inflammation

The intestinal epithelium, particularly in the colon, is permanently in close association with a myriad of microbes and their products. Therefore, the enterocytes must sense and respond appropriately to this potential immunological challenge of the luminal content. This leads to a normal physiological state of controlled low-grade inflammation.[93] However, mechanisms that allow individuals to tolerate commensal microbes, and thus limit the inflammatory response, are not yet completely understood. In some conditions, such as inflammatory bowel disease, this immunological control is thought to be disturbed.[94]

Several studies, both *in vitro* and *in vivo*, indicate that bacterial metabolites such as butyrate may affect the host immune response. As butyrate is known to be an important energy source for the colonic epithelium, it has been hypothesized that a lack of luminal SCFAs or the inability to oxidize butyrate leads to a nutritional deficiency of the colonic epithelium, causing mucosal atrophy in short term and 'nutritional colitis' in long term.[95] Possible changes in intestinal butyrate concentrations and/or oxidation of butyrate have been reported in diversion colitis and UC. Diversion colitis may occur as complication after a surgically diverted intestine (e.g. Hartmann's procedure), and is characterized by severely decreased luminal concentrations of SCFAs of 0, 4 and 0.8 mM for acetate, propionate and butyrate, respectively, measured in the bypassed part of the rectosigmoid.[96] UC is an inflammatory bowel disease, characterized by alternating periods of flare ups and quiescent disease.[97] Increased[95, 98] as well as decreased[99, 100] faecal concentrations of butyrate have been reported in patients with active UC, but these were never as low as in diversion colitis.[96] In addition, a diminished capacity of the intestinal mucosa to oxidize butyrate has been reported in patients with active UC.[101, 102] In patients with inactive UC, however, a normal butyrate oxidation has been found *in vivo,*[101, 103] which suggests that abnormal butyrate oxidation is not a primary defect in colon mucosa of UC patients. A possible explanation for the decreased oxidation in UC patients was proposed by Nancey *et al.* who showed that butyrate oxidation could be reduced by TNFα at concentrations found in inflamed human mucosa.[104] It has also been reported that butyrate oxidation in colonocytes can be inhibited by hydrogen sulphide *in vitro.*[105] Increased luminal concentrations

of sulphide as well as high numbers of sulphate-reducing bacteria have been reported in UC patients.[105], [106] However, evidence for hydrogen sulphide as a metabolic toxin in UC *in vivo* remains limited.[105]-[108]

Intervention studies

Several animal studies have been performed to evaluate the effects of butyrate on inflammation and preventive as well as therapeutic effects have been reported.[109]-[112]

Human studies analysing the effects of SCFAs were performed in patients with colonic inflammation using rectal enemas containing SCFA mixtures or butyrate alone (Table 1).[45], [46], [73], [96], [113]-[126]

Table 1. Studies performed using butyrate and/or SCFA enemas in different patient groups

Patients	*n*	Enema treatment	Results	Reference
Active distal UC	10	100 mM butyrate and placebo 100 mL, pH = 7, b.d. for 2 weeks. Wash out: 2 weeks	Butyrate → stool frequency↓, blood discharge↓ and endoscopic and histological scores↓	45
	45	CS, 5-ASA or 130 mM SCFA (46:23:31*) 60 mL, pH = 7, b.d. for 6 weeks	SCFAs equally efficacious to CS or 5-ASA	120
	40	150 mM SCFA (53:20:27) vs. placebo 100 mL b.d. for 6 weeks	SCFAs → intestinal bleeding↓, urgency↓ and patient self-evaluation score↑	126
	47	130 mM SCFA (46:23:31) vs. 100 mM butyrate vs. placebo 60 mL, pH = 5.5, b.d. for 4–8 weeks	No differences between groups. Butyrate for 8 weeks → fewer colonic segments affected endoscopically	118
	38	80 mM butyrate vs. placebo 60 mL, pH = 7 for	No differences between butyrate and placebo treatment	121

* Ratio = acetate:propionate:butyrate.

SCFA, short-chain fatty acid; CS, corticosteroid; 5-ASA, 5-aminosalicylic acid; b.d., twice daily.

Most of these studies focussed on UC patients with moderate to active disease. Although some controlled studies with enemas containing butyrate or SCFA mixtures in UC patients did not find beneficial effects[121] or only trends towards clinical improvement,[46], [118], [119] various other studies revealed a significant improvement in clinical and inflammatory parameters.[45], [115], [120], [124], [126] Studies in patients with diversion colitis reported inconsistent results with regard to improvement in clinical symptoms and inflammatory parameters in response to administration of mixtures of SCFAs vs. placebo.[96], [114] Two other human intervention studies determined mucosal cell proliferation in patients after Hartmann's procedure and found trophic effects of SCFA mixtures in the mucosa of the closed rectal and sigmoid segment.[73], [116]

The effects of butyrate containing enemas on radiation proctitis[113], [117], [122], [125] and pouchitis[123] have been studied in small groups and besides one report[125] that showed that butyrate was an effective treatment of radiation proctitis, other studies did not report clear-cut beneficial effects of SCFA irrigation in these two patient groups.[113], [117], [122], [123]

The equivocal results in human intervention studies using enemas may partly be explained by differences in treatment duration, butyrate enemas vs. SCFA enemas, differences in concentrations and volumes of these SCFAs and the small number of patients included. Moreover, some studies suffered from methodological limitations such as a crossover design with insufficient wash-out time that may have resulted in differences in pre-treatment levels between groups (Table 1).

As there are limitations to prolonged use of rectal enemas, especially with regard to the compliance, oral ingestion of fermentable dietary fibre and the use of enteric-coated tablets containing butyrate have been explored. Administration of such tablets (4 g of butyrate daily) in combination with mesalazine vs. mesalazine alone, significantly improved the disease activity score in patients with mild-to-moderate UC.[41] Similar butyrate tablets also resulted in a significant clinical improvement in Crohn's disease patients, but this study lacked a control group.[127]

The effects of fermentable fibre supplementations, such as germinated barley foodstuff,[128]-[130] inulin,[131], [132] psyllium[133], [134] and oat bran,[9] which increase faecal butyrate concentrations, have also been studied in several clinical trials. Germinated barley foodstuff prolonged remission in inactive UC patients[128] and attenuated clinical activity in active UC patients.[129], [130] Inulin supplementation resulted in a decreased mucosal inflammation of the ileal reservoir in patients with an ileal-anal pouch anastomosis[132] and lowered faecal calprotectin

concentrations in patients with active UC.[131] Two other studies in UC patients in remission, evaluating the supplementation of psyllium and oat bran, showed that the supplementation was safe, increased faecal butyrate concentrations and were found to be effective in the maintenance of remission.[9], [133], [134] However, this effectiveness should be confirmed in larger clinical trials.

Although not all studies in patients with colonic inflammation confirmed the reduction in inflammation and clinical symptoms as a result of luminal administration of butyrate or stimulation of luminal butyrate production by the ingestion of dietary fibre, an amelioration of the inflammation and symptoms in active UC patients is strongly suggested. In addition, butyrate might play a role in the prevention of inflammation as supported by the results with UC patients in remission.

Mechanisms of butyrate's anti-inflammatory effect

Apart from being an important energy source for the colonocytes, butyrate can exert direct immuno-modulatory effects.[111], [115], [135] Suppression of nuclear factor kappa B (NF-κB) activation, which may result from the inhibition of HDAC, is the most frequently studied anti-inflammatory effect of butyrate.[136], [137]

Nuclear factor-κB is a transcription factor that controls the expression of genes encoding proinflammatory cytokines, chemokines, inducible inflammatory enzymes such as inducible NO synthase and cyclo-oxygenase-2, adhesion molecules, growth factors, some acute phase proteins and immune receptors.[138] In a study with UC patients, the increased mucosal levels of activated NF-κB were reduced by butyrate and this correlated with a decrease in the disease activity index and the numbers of infiltrated neutrophils and lymphocytes.[115] This anti-inflammatory effect of butyrate via NF-κB inhibition, contributing, for example, to decreased concentrations of myloperoxidase, cyclo-oxygenase-2, adhesion molecules and different cytokine levels, has been confirmed in several *in vitro* and *in vivo* studies.[109], [111], [112]

Apart from inhibition of NF-κB activation, butyrate may exert an anti-inflammatory activity through inhibition of the interferon-γ production and/or signalling[139], [140] and the upregulation of peroxisome proliferator-activated receptor-γ (PPARγ).[141]-[145] PPARγ is a ligand-activated transcription factor that is highly expressed in colonic epithelial cells and its activation is thought to exert anti-inflammatory effects.[146] PPARγ protein expression is 60% lower in the non-inflamed colonic mucosa of UC patients compared with that in controls.[147] Modulation of PPARγ protein expression in UC may prove to be an interesting treatment for UC.

Finally, butyrate as well as other SCFAs can act as signalling molecules through specific G-protein-coupled receptors, GPR41 and GPR43, identified for SCFAs.[148]-[150] These two SCFA receptors are expressed on immune cells, particularly polymorphonuclear leucocytes, and are

also highly present in the colonic mucosa.[151] It has been hypothesized that these receptors play a role in the immune surveillance of the colonic mucosa towards microbial activity.[149-151]

In conclusion, several mechanisms for the anti-inflammatory activity of butyrate have been described, which can contribute to the observed clinical effectiveness of colonic butyrate supplementation on colonic inflammation.

Butyrate and oxidative stress

As described above, butyrate may influence the inflammatory process and the initiation and progression of carcinogenesis. In both these processes, oxidative stress is involved.[152, 153] Oxidative stress is the result of an imbalance between the generation of reactive oxygen and reactive nitrogen species and the antioxidant defence mechanisms, resulting in a cascade of reactions in which lipids, proteins and DNA may be damaged. Neutrophilic granulocytes are an important source of potent oxidizing species in the inflamed colon.[152]

There is some evidence that butyrate is able to modulate oxidative stress. In two studies, preincubation of isolated rat[154] or human[155] colonocytes with butyrate showed a significant reduction in H_2O_2-induced DNA damage. In rats, resistant starch intake decreased the levels of colonocyte DNA damage induced by a high protein diet. This DNA damage correlated negatively with caecal butyrate concentrations.[156]

The mechanism by which butyrate reduces oxidative stress remains unknown. Scavenger activity of butyrate is unlikely because of its chemical structure. However, butyrate may affect DNA repair systems and levels of enzymatic or non-enzymatic (anti)oxidant systems. For example, fermentable fibre supplementation resulted in a decreased colonic myeloperoxidase activity and a restoration of the colonic concentration of the antioxidant glutathione in a rat model of TNBS-induced colitis.[122] In addition, butyrate enhanced the activity of glutathione-*S*-transferase in HT-29 cells[88] and increased catalase activity in artery smooth muscle cells of rats.[157]

Although human *in vivo* data are not yet available, butyrate may enhance the protection against mucosal oxidative stress by affecting the activity of intracellular antioxidants, DNA repair systems or (anti)oxidant enzymes.

Butyrate and the colonic defence barrier

Besides the effects of butyrate on carcinogenesis, inflammation and oxidative stress, butyrate has been shown to affect several components of the colonic defence barrier leading to enhanced protection against luminal antigens. One important component of this barrier is the mucous layer covering the epithelial lining consisting of mainly mucin glycoproteins and trefoil

factors (TFFs). Mucin glycoproteins are classified into neutral and acidic subtypes and the latter category further includes sulfomucins and sialomucins. Sulphated mucins are generally considered to be more resistant to bacterial degradation.[158] Several epithelial mucin (MUC) genes have been identified in humans, of which MUC2 is predominantly expressed in the human colon.[159] Alterations in goblet cell function, composition and thickness of the intestinal mucous layer have been found in several intestinal disorders. For example, a reduced mucous thickness and a decreased MUC2 production have been reported in UC patients.[160]

In *in vitro* studies, butyrate increased the MUC2 gene expression in specific cell lines.[161]-[164] In addition, 0.1–1 mM butyrate administered to human colonic biopsy specimens *ex vivo* stimulated mucin synthesis.[165] Luminal butyrate administration of 5 mM, but not 100 mM, increased mucous secretion in an isolated perfused rat colon.[166] In another rat study, caecal and faecal SCFA concentrations were found to correlate with mucous thickness. In humans, effects of butyrate alone on mucous synthesis, thickness of the mucous layer and MUC expression *in vivo* have not been reported.

The effects of a number of fermentable dietary fibres on the mucous layer have been studied with varying results. For example, resistant starch increased the number of acidic mucins, but did not affect the number of goblet cells in rats.[61] In contrast, fructo-oligosaccharides (FOS) increased the number of goblet cells in piglets.[167] In a human intervention study with patients with an ileo-anal pouch, inulin supplementation did not alter MUC2 expression or the ratio between sulfomucins and sialomucins.[168]

Trefoil factors are mucin-associated peptides that contribute to the viscoelastic properties of the mucous layer. TFFs are thought to reduce the recruitment of inflammatory cells and to be involved in the maintenance and repair of the intestinal mucosa, although the exact mechanism for this effect is not yet known.[169] Intestinal trefoil factor (ITF or TFF3) is almost exclusively secreted by the intestinal goblet cells.[170] In a rat TNBS model of colitis, TFF3 expression was decreased during active disease, and intracolonic administration of butyrate increased TFF3 expression.[112], [171] However, butyrate inhibited the expression of TFF3 in colon cancer cell lines[172], [173] and in colonic tissue of newborn rats.[172]

Other components of the colonic defence barrier that are involved in the maintenance of the colonic barrier, which may be influenced by butyrate are transglutaminase, antimicrobial peptides and heat shock proteins (HSPs).

The enzyme transglutaminase is actively involved in intestinal mucosal healing and correlates with the severity of inflammation in UC.[174] In a rat model of colitis, butyrate restored the colonic transglutaminase levels.[62], [175] Antimicrobial peptides such as cathelicidin (LL-37) and defensins, protect the gastrointestinal mucosa against the invasion and adherence of bacteria and thereby prevent infection.[176]-[178] Several *in vitro* studies have shown that butyrate

upregulates the expression of LL-37 in different colon epithelial cell lines as well as in freshly isolated colorectal epithelial cells.[179] HSPs confer protection against inflammation by suppressing the production of inflammatory modulators.[180], [181] Butyrate induced the expression of HSP70 and HSP25 in Caco-2 cells[181] and in rats.[61], [180], [182] However, in a study in rats with DSS-induced colitis, butyrate inhibited HSP70 expression. This was related to protection against the decrease in cell viability, increase in mucosal permeability and neutrophil infiltration in DSS colitis. It was concluded that the induction of heat shock response has a protective effect before an injury, whereas activation of heat shock response leads to cytotoxic effects after a proinflammatory stimulus.[183]

In addition, there is evidence from *in vitro* studies with human colon cancer cell lines that butyrate is involved in repair after mucosal damage through an increase in the rate of cell migration. Efficient repair of superficial injuries and mucosal ulcers is important in maintaining and re-establishing the epithelial barrier.[184]

In conclusion, there are several lines of evidence suggesting that butyrate reinforces the colonic defence barrier by affecting several components of this barrier, such as the promotion of epithelial migration and the induction of mucins, TFF, transglutaminase activity, antimicrobial peptides and HSPs. However, most of these effects still have to be confirmed in the human situation.

Butyrate and intestinal epithelial permeability

Intestinal epithelial permeability has been widely studied as an important parameter of the intestinal defence barrier. Under normal conditions, the epithelium provides a highly selective barrier that prevents the passage of toxic and proinflammatory molecules from the external milieu into the submucosa and systemic circulation. Macromolecules pass the epithelial barrier mainly via the paracellular route for which tight junctions are the rate-limiting structures.[185] Increased permeability, indicating impaired epithelial barrier function, is thought to be involved in the pathophysiology of several gastrointestinal inflammatory diseases, but can either be a cause or a consequence of inflammation.[186]

Several studies have assessed the effects of butyrate on intestinal permeability *in vitro* as well as *ex vivo*. At low concentrations, butyrate (up to 2 mM) induces a concentration-dependent reversible decrease in permeability in a Caco-2 and HT-29 cell lines.[187], [188] This decrease in permeability may be related to the butyrate associated increased expression of tight junction proteins observed in different cultured cell lines, but this effect was shown to be cell type dependent.[189], [190] At higher concentrations (8 mM), however, butyrate increased the permeability in a Caco-2 cell line.[188] An *ex vivo* study, using adult rat distal colon mucosa mounted in an Ussing chamber, demonstrated that acute exposure to butyrate at a concentration of 10 mM, but not 1 or 5 mM increased paracellular permeability in rat

colon.[191] This has also been demonstrated in rats fed a diet-containing fermentable FOS. The rapid bacterial fermentation of FOS led to accumulation of high concentrations of SCFAs that increased intestinal permeability and was associated with increased translocation of *Salmonella*.[192] However, in humans, daily FOS supplementation of 20 g did not increase intestinal permeability.[193]

It can be concluded that the effect of butyrate on intestinal permeability depends on its concentration and on the model system or species used. The effects of butyrate at different concentrations remain to be evaluated in the human *in vivo* situation.

Butyrate and satiety

It has been hypothesized that SCFAs produced in the large intestine also can influence upper gut motility and satiety.[194] Endocrine L-cells present in large concentrations in the colonic mucosa secrete peptides such as glucagon-like peptide 1 (GLP-1), peptide YY (PYY) and oxyntomodulin, which are involved in appetite regulation.[195] In several animal studies using fermentable carbohydrates such as inulin,[195] lactitol[196] and FOS,[197], [198] an increased satiety, decreased weight gain and increased endogenous production of GLP-1 and/or PYY were reported. In humans, FOS increased satiety[199] and increased plasma GLP-1 concentrations.[200] However, lactitol did not affect plasma concentrations of this gut peptide.[196]

The increased satiety is possibly promoted through the production of SCFAs. This is supported by a number of studies. Butyrate increased the expression of PYY and proglucagon *in vitro* in rat epithelial cells[201] and increased PYY release, but not that of GLP-1, in the isolated colon of rats[202], [203] and rabbits.[204] In addition, colonic SCFA infusion in rats stimulated PYY release.[205] However, colonic infusion with SCFAs in humans did not increase plasma levels of either PYY or GLP-1.[206] Activation of the SCFA receptor GPR43 expressed in endocrine L-cells may play a role in this effect on satiety.[148]

There is increasing evidence that the effect of fermentable dietary fibre on satiety is mediated through the colonic production of SCFAs. However, most evidence originates from rat studies, while again human evidence remains limited.

Adverse effects of butyrate

In contrast to the wide range of positive effects of butyrate on the intestinal mucosa, a small number of studies have also shown some adverse effects. Two rat studies revealed that rectal administration of butyrate (8–1000 mM), dose dependently increased colonic visceral sensitivity.[207], [208] However, these effects have not yet been reported in humans.

In faeces of weaning children, low butyrate concentrations have been measured.[209] It has been hypothesized that overproduction or accumulation of SCFAs may be toxic to the intestinal

mucosa of premature infants and might play a role in the pathogenesis of neonatal necrotizing enterocolitis. It has been demonstrated that the severity of mucosal injury to butyrate, measured in newborn rats, was dose dependent and also depended on the maturation of the intestine.[172], [210], [211] It remains to be established whether luminal butyrate in premature infants can increase towards levels that are toxic for the intestinal mucosa.[211] In addition, as mentioned before, increased permeability and *Salmonella* translocation has been found after FOS supplementation in a study with rats, which may be the result of SCFA accumulation.[192] However, this was not confirmed in the human situation.[193]

Conclusions

Short-chain fatty acids are important end-products of microbial fermentation. Among the SCFAs produced in the human intestine, butyrate has been widely studied and has been shown to play an important role in the maintenance of colonic health. Increased butyrate production in the large intestine seems to be responsible for at least some of the protective effects of fermentable dietary fibre. However, it should be taken into account that the effects of increased butyrate production may be accompanied by other effects of dietary fibres and its fermentation, such as changes in the composition of the intestinal microbiota and increased faecal bulking.

The effects of butyrate are diverse and complex and involve several distinct mechanisms that go beyond the classical impact as an energy source for the intestinal epithelial cells. Frequently described are the effect on gene expression because of the inhibition of histone deacetylase and the suppression of NF-κB activation. Hence, butyrate exerts multiple effects such as the inhibition of colonic carcinogenesis, inflammation and oxidative stress, the improvement of the colonic defence barrier function and the promotion of satiety.

It should, however, be noted that also some equivocal results have been reported, which partly can be explained by the different butyrate concentrations and models used. In addition, a few animal and *in vitro* studies demonstrate negative effects at higher butyrate concentrations on permeability and visceral sensitivity of the large intestine.

In conclusion, in the last decade, several new insights into possible mechanisms and effects revealed that butyrate is a pivotal metabolite produced within the large intestine. However, these new insights are mainly based on *in vitro* data, animal models and some clinical intervention studies. More emphasis should be placed on human *in vivo* studies to elucidate the role of butyrate in health and disease.

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