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ORIGINAL CONTRIBUTION

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Rationale for the luminal provision of butyrate in intestinal diseases

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Dedicated to Wolfgang F. Caspary on the occasion of his 60th birthday

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Summary Short chain fatty acids (SCFA), especially butyrate, play central metabolic roles in maintaining the mucosal barrier in the gut. A lack of SCFA, leading to endogenous starvation of enterocytes, may be the cause of ulcerative colitis and other inflammatory conditions. The main source of SCFA is dietary fibre, but they can also be derived from structured lipids, e. g. tributyrin. Once absorbed by non-ionic diffusion or carrier-mediated anion exchanges, SCFA are either used locally as fuel for the enterocytes or enter the portal bloodstream. Butyrate has been shown to increase wound healing and to reduce inflammation in the small intestine. In the colon, butyrate is the dominant energy source for epithelial cells and affects cellular proliferation and differentiation by yet unknown mechanisms. Recent data suggest that the luminal provision of butyrate may be an appropriate means to improve wound healing in intestinal surgery and to ameliorate symptoms of inflammatory bowel diseases.

Key words Butyrate – differentiation – inflammatory bowel disease – structured lipids

Introduction: pathophysiology of the mucosal barrier in intestinal diseases

Epithelial cells form a diaphoneous layer between the reductive environment of the lumen and the oxidative environment of the lamina propria [1]. The cellular metabolisms involved in the barrier function of epithelial cells include substrate breakdown, the ability to assemble cell membranes, the detoxification of luminal agents and mechanisms to uphold a redox balance between the adjoining oxidative and reductive environments [2]. Epithelial injury by physiological or pathological insults may result in uncontrolled and excessive exposure of antigenic, toxic, immunoadjuvant, and chemotactic factors to the host immune system [3, 4]. In all these functions short-chain fatty acids (SCFA) play a central metabolic role in upholding a dynamic epithelial cell barrier in the gut and to restore repair mechanisms which are likely to be essential for the prevention or resolution of inflammation [2, 4, 5]. These C2-C5 organic fatty acids are formed in the gastrointestinal tract of mammals as a result of anaerobic bacterial fermentation of undigested dietary components and are avidly absorbed by the colonic epithelium [6].

In colonocytes, fatty-acid oxidation governs processes such as ATP generation, lipogenesis, absorption of sodium, detoxification of xenobiotics and acetylation of histones. It is known that butyrate is the primary metabolic fuel for colonocytes, predominantly in the distal colon [7]. A lack of SCFA can lead to colonic inflammation, such as diversion colitis and pseudomembranous colitis [5]. Moreover, a series of experimental results verifies the role of butyrate in the pathogenesis of other types of colonic inflammation, such as ulcerative colitis, which may be associated with a mucosal defect in the metabolism of SCFA. It is postulated that ulcerative colitis is due to either exogenous (decreased luminal availability) or endogenous (impaired intracellular oxidation of butyrate) starvational factors limiting fatty-acid oxidation in colonocytes [2, 7]. One possible explanation for the impaired butyrate metabolism could be the presence of reducing sulphur substrates, produced by sulphur reducing bacteria in the colon [8]. These sulphur sub-

strates might inactivate fatty-acid dehydrogenases or butyryl-CoA synthetase [2]. In several studies β-oxidation was found to be significantly reduced and sulphur-reducing bacteria were increased in colonocytes of acute and quiescent ulcerative colitis [2, 9]. This was true for diseased as well as for uninvolved segments [2]. These findings suggest that changes in β-oxidation precede the onset of overt colitis. Diminished fatty-acid oxidation and subsequent energy deficiency would lead to a breached barrier of colonic epithelial cells and immune changes [2].

The use of SCFA enemas in distal ulcerative colitis and other forms of inflammation is based on the assumption that epithelial energy deficiency may be an important factor in the pathogenesis of these diseases and that the supply of the preferred nutrients, i. e. by raising the luminal butyrate concentration above normal, may ameliorate inflammations [7]. Thus, therapeutic agents influencing or probably reversing the inhibition of fatty-acid oxidation represent promising targets of future research.

Butyrate, a nutriceutical for maintenance and regeneration of the mucosal barrier in intestinal diseases

Nutritional uptake of butyrate

Dietary fibre as precursor of butyrate

The total concentration and relative molar concentrations of individual SCFA are greatly influenced by the diet. Therefore, it may be possible to manipulate different dietary substrates to achieve desired amounts and ratios of SCFA, particularly with respect to butyrate, in order to influence the incidence of colonic diseases [6]. Dietary fibre is the principal substrate for the fermentation of SCFA in humans; however, undigested starch, protein, mucus, shed epithelial cells and gastrointestinal secretions also contribute to their production [6, 10]. Besides SCFA, hydrogen, methane and carbon dioxide are produced by anaerobic bacteria in the large intestine [11]. The type of dietary fibre determines the rate and degree of fermentation: insoluble fibre is resistant to colonic microflora fermentation and contributes greatly to faecal bulk. This type of fibre includes cellulose and lignin, of which only 5–20 % undergo anaerobic fermentation in the colon. In contrast, water-soluble fibre such as pectin is almost completely fermented by colonic microflora [10]. Resistant starches make up 10–20 % of all starch in the Western diet. The proportion of resistant starch ranges from 75 % in green bananas, to 2–10 % in bread, to less than 1 % in cooked rice [10, 12]. Sugars like lactose, raffinose and stachyose may not be absorbed in the small intestine and enter the colon. Therefore, diets high in fibre, resistant starches and complex carbohydrates will lead to an increased rate of SCFA fermentation [10].

Based on a normal diet and on the amount of bacterial cells produced in the colon, one can estimate that about 15–60 g carbohydrate is fermented per day, yielding 150–600 mmol SCFA [9, 13]. The average intraluminal concentration of SCFA has been estimated to be between 100 and 170 mM [14], while the highest microbial SCFA production is found in the caecum, followed by the colonic contents [15–17]. Butyrate, representing approximately 15 % of the colonic SCFA, reaches concentrations up to 20 mM in the colon and faeces of animals and man [8, 18]. In the adult human with a faecal output of 80–230 g/day only 5–20 mmol/day is excreted so most SCFA (95 %) is absorbed [9, 13]. In industrial countries SCFA make up about 5–15 % of the total energy uptake, whereas in less developed countries this number may be even higher [9].

Short chain fatty acids

A direct source of butyrate is the diet, where it is present at low levels in many fruits and vegetables, but its richest source is from milk fat (butter) which contains 3–4 % butyrate as glycerol esters, termed tributyrin [18]. The high butyrate content in milk and dairy products is due to a significant production of SCFA in the forestomach of ruminants. Most of these SCFA are directly absorbed into the bloodstream to be available for use by the tissues and partly enter the milk [19].

Structured lipids

Another possible source of butyrate are structured lipids, e. g. SCFA-containing triglycerides (SCT). Butyryl triglyceride (tributyrin or glyceryl tributyrate) is a SCT with butyrate esterified at the 1, 2, and 3 positions and a candidate precursor for butyrate that could be administered orally [18]. Like triacetin it is neutral, chemically stable, and rapidly hydrolysed by pancreatic and gastric lipases to glycerol and their respective even-numbered SCFA, butyrate or – in the case of triacetin – acetate. Parenterally administered SCTs are readily hydrolised to glycerol and free fatty acids in the bloodstream [20]. In contrast to tributyrin, triacetin is water-soluble and does not require emulsification, which makes it a very versatile, alternative energy source to be incorporated into parenteral nutrition (TPN) or total enteral nutrition regimens. Alternatively, triacetin could be combined with aqueous solutions of dextrose and water for peripheral vein delivery of calories. Triacetin has been shown to be metabolically beneficial in hypermetabolic states, improving protein metabolism and reducing intestinal atrophy [21]. Studies to evaluate TPN with combinations of tributyrin or tripropionin are still in progress.

Regarding enteral nutrition, a chemically defined diet containing 40 % of nonprotein as SCTs (1:1 triacetin and tributyrin, wt:wt) instead of long-chain or medium-chain

fatty acids has been shown to maintain body weight, nitrogen balance, and liver function. The enteral administration of SCTs to either small or large bowel may provide a useful alternative therapy in patients with intestinal loss due to injury (e. g. short bowel syndrome) or disease (e. g. inflammatory bowel syndrome) [20, 21].

Digestion and absorption of butyrate

Short chain fatty acids, mainly acetate, propionate and butyrate (60:25:15), are produced in the large intestine in substantial amounts, rapidly absorbed and subsequently utilised as a substrate of energy metabolism [8, 22]. Mechanisms involved in the transport of SCFA in the large intestine are dose-dependent and include several transcellular processes [9, 22]. Protonated SCFA are lipid soluble and readily diffuse across cell membranes, whereas the ionized form (at normal pH approximately 95 %) is not lipid soluble and thus requires different pathways across the epithelium (Fig. 1) [8, 10, 23–25].

Recent studies reveal that in addition to non-ionic diffusion a considerable amount of SCFA is transported by carrier-mediated SCFA anion exchanges with bicarbonate [8, 22]. This SCFA:HCO_3 exchange can be found in apical as well as in basolateral membranes, differing in kinetic characteristics but sharing a high degree of specificity for C2-C5 fatty acids [10]. Additionally, an interaction between SCFA and Na^+ transport has been observed, in which Na+ absorption may stimulate SCFA absorption [8, 22]. When SCFA enter the cell by non-ionic diffusion, they rapidly dissociate. Subsequently, the basolateral sodium-proton exchange is turned on in response to the intracellular proton load to keep the intracellular pH constant [26]. Sodium is then excluded from the cell by the basolateral Na^+–K^+–ATPase. Due to an effective pH regulation mechanism in the basolateral membrane, SCFA absorption does not change the pH of enterocytes in the large intestine [22]. Thus, SCFA contribute to a basal physiological function of the colon, which is a conservation of Na^+ and H_2O [9]. Paracellular transport of SCFA anions is not of significance under physiological conditions [22]. If the capacity of colonic flora to metabolise carbohydrates is overwhelmed or if antibiotics are given, carbohydrates remain in the colonic lumen, which lacks any appropriate nutrient absorptive pathway, and an osmotic diarrhoea may occur [10].

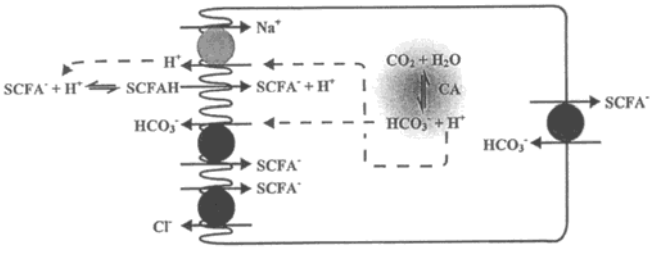

Fig. 1 Model for cellular mechanisms involved in absorption of short chain fatty acids (SCFA) in the human colon [8].

Studies to determine the jejunal absorption of acetate, propionate and butyrate showed that these three SCFA were also absorbed rapidly and at equal rates in the small intestine in a dose-dependent manner and reached saturation at higher concentrations. Water and sodium absorption increased slightly during butyrate absorption [27].

Metabolism of butyrate

Once the SCFA are absorbed by the colonocyte, they are either locally used as fuel for the colonic mucosal epithelial cells, or enter the portal bloodstream. Butyrate is the dominant energy source for colonic mucosal enterocytes, accounting for 70 % of their oxygen consumption [28, 29]. Of butyrate produced in the colon 70–90 % is metabolised by the colonocyte. Butyrate is used preferentially over propionate and acetate in a ratio of 90:30:50 [8, 10], and the dependence of the colon on SCFA oxidation increases from the caecum to rectum. Acetate and propionate are less avidly metabolised than butyrate and are transported to the liver [10].

In epithelial cells, butyrate is metabolised via β-oxidation in the Lynen circle (Fig. 2) [8]. This initially involves conversion to buturyl-CoA by the enzyme butyryl-CoA-synthetase and, in a series of reactions, a rapid conversion to acetyl-CoA. In the liver, longer chain fatty acids or ketone bodies can be generated as well. At least one fifth of intravenously injected butyrate has been reported to be used for hepatic ketogenesis in sheep, with the remainder presumably oxidised or used as the primer compound for long chain fatty acid synthesis. Although nearly all the butyrate is taken up by epithelial tissues of the digestive tract and by the liver, trace amounts can enter the general blood circulation, particularly after large meals and extensive fermentation in the digestive tract. Nearly all tissues of the body have the ability to metabolise butyrate. In peripheral tissues, butyrate is rapidly oxidised or used in lipogenesis; it also is removed from the bloodstream by the mammary gland mainly for milk fat synthesis [30].

Butyrate effects and mechanisms

Small intestine

The epithelial cells of the small and large intestine generate their energy sources mainly from the site of the lumen. In contrast to the colon epithelium, the mucosa of jejunum and ileum is less dependent on luminal nutrition, with glutamine and glucose being their main energy sources. In times of starvation, the lack of luminal nutrition can be

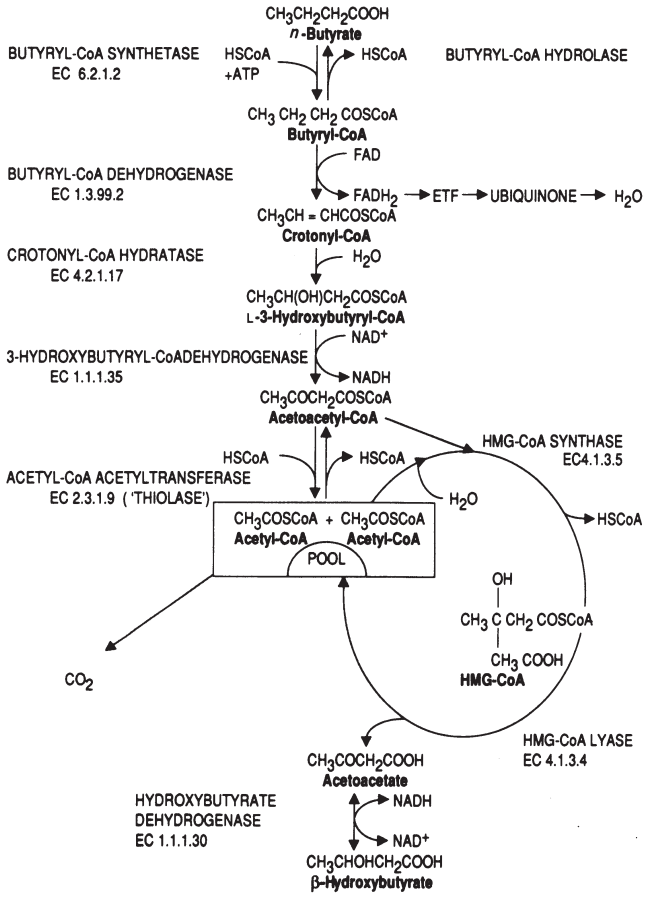

Fig. 2 β-Oxidation pathway of butyrate in the HMG-CoA-cycle (Lynen-cycle) [2].

compensated by glutamine from skeletal muscle or ketone bodies derived from the breakdown of long chain fatty acids, whereas in the colonic mucosa functional and morphological changes occur in an early state of nutrient deficiency [9].

However, butyrate has also been shown to have a beneficial effect on the small intestine. In experimental studies the oral administration of short chain fatty acids close to physiological concentrations reduced intestinal mucositis caused by treatment with the cytostatic drug Ara-C in mice fed commercial or elemental diets. Protein and nucleotide concentrations in the intestinal mucosa were higher in the group receiving SCFA than in the control group receiving placebo, and there was an increase in the height of intestinal villi, with no alterations in the crypt compartments [31]. This is consistent with the finding of *in vitro* studies, showing increased cell migration in wounded *in vitro* models of intestinal epithelium after treatment with SCFA [4]. As rapid growth of mucosa is especially important to the intestinal anastomosis, SCFA, especially butyrate, can serve to enhance postresectional epithelial proliferation in both the small bowel and the colon [5, 32]. Mechanisms by which SCFA may mediate intestinal proliferation and function include provision of energy, stimulation of blood flow, production of exocrine pancreatic secretions, stimulation of the autonomic nervous system, and production of enterotrophic gastrointestinal hormones [5]. These data suggest that the oral administration of SCFA may be an appropriate means to increase wound healing of epithelial cells and to reduce inflammation and necrosis due to cytostatic drug administration [31].

On the other hand, the lack of butyrate in the medium of intestinal tissue is associated with a rapid induction of apoptosis, accompanied by typical apoptotic features like nuclear chromatin condensation, cytoplasmatic bebbling, cell shrinking, and internucleosomal DNA fragmentation. In one study, the induction and manifestation of apoptosis occurred already 45 min after removal of butyrate. The molecular mechanism underlying this apoptotic process of butyrate-deprived enterocytes included the induction of Bax, a proapoptotic protein, whereas the expression of Bcl–2, an anti-apoptotic protein, remained unchanged. Furthermore, Bax showed to accumulate preferably in the epithelial surface after butyrate deprivation [33]. Additionally, SCFA have been shown to modulate gastrointestinal motility and therefore can be considered as luminal chemical stimuli, which contribute to the regulation of digestive motility. In the ileum, they elicit contractile activity and consequently might limit the extent of the colo-ileal reflux [34].

In summary, the presence of butyrate in the small intestine may be an essential factor in maintenance and healing of healthy mucosa and an appropriate substance – probably even more efficient than glutamine – for the improvement of patients with mucositis caused by cancer treatment.

Colon

Butyrate serves as an energy yielding substrate in the colonocytes and, additionally, affects several cellular functions like proliferation and differentiation. A disruption of the balance between cell gain through mitosis and cell loss through programmed cell death (apoptosis) is thought to be an important event in carcinogenesis [35]. Butyrate stimulates proliferation in the basal crypt departments *in vitro* without increasing cell labelling in the upper crypt, which is considered a preneoplastic biomarker (Fig. 3) [36]. On the contrary, a reduction in concentration of luminal butyrate by decreased delivery of fermentable substrate to the large intestine induces mucosal atrophy, which is reversible by instillation of SCFA, especially butyrate, into the colonic lumen [6].

The mechanisms by which butyrate enhances normal colonic mucosal proliferation are not well understood, but they appear to be indirectly and directly mediated. Butyrate exerts indirect systemic effects, as colonic instillation of SCFA stimulates proliferation not only in colonic mucosa,

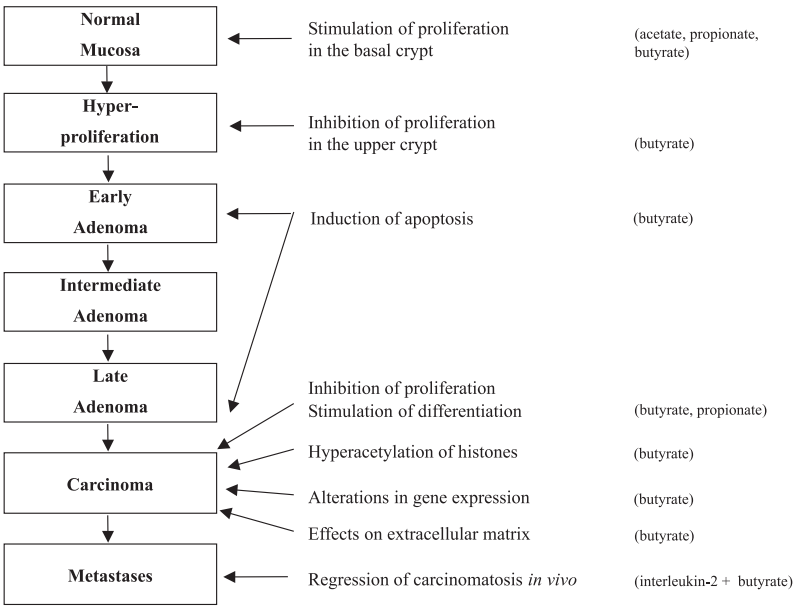

Fig. 3 Effects of short-chain fatty acids (SCFA) on colonic epithelial cells at different stages of the adenoma-carcinoma sequence [35].

but also in unexposed, adjacent colonic epithelium, ileum and jejunum. Additionally, butyrate directly affects proliferation in short-term organ culture of human colonic mucosa in the absence of circulating neural factors [6]. The mechanism for locally mediated colonotrophism seems to be multifactorial and may include increases in visceral blood flow, aerobic oxidation of SCFA for energy, increased production of enterotropic hormones, and stimulation of the enteric nervous system (Fig. 4) [5, 10].

While butyrate increases proliferation of normal colonic epithelium, it decreases proliferation of neoplastic colonocytes *in vitro* and *in vivo* [35]. Butyrate inhibits DNA synthesis and arrests the growth of neoplastic colonocytes in the G1 phase of the cell cycle in concentrations that are not toxic to the cells. These effects can be reversed by simple removal of butyrate from the culture medium [6]. Furthermore, butyrate has been shown to induce differentiation and apoptosis of neoplastic colono-

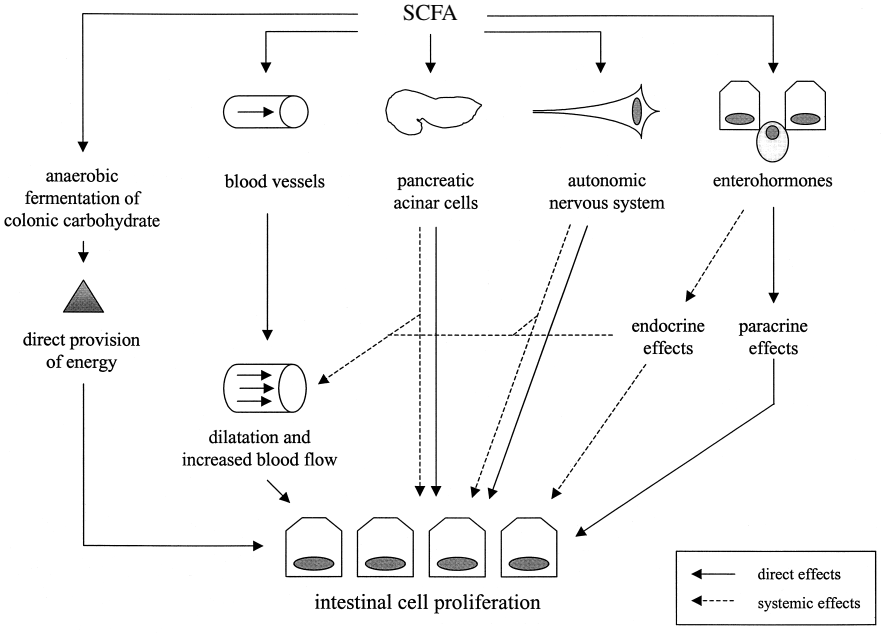

Fig. 4 Possible mechanisms by which short-chain fatty acids (SCFA) may mediate intestinal proliferation and function [modified from 5].

cytes *in vitro* and *in vivo*, whereas it does not significantly affect the expression of differentiation markers, like alkaline phosphatase, in normal colonocytes *in vitro* and *in vivo* [6, 14, 29]. Thus, butyrate seems to be an important mediator in the different stages of the adenoma-carcinoma sequence (Fig. 3) where a switch from stimulation to suppression of cell proliferation must occur [10, 35].

The paradoxical effects of butyrate on normal and neoplastic colonocyte proliferation and differentiation are not fully understood. Mechanisms that have been proposed for the butyrate-mediated effects, include hyperacetylation of histones due to inhibition of histone deacetylase, which leads to increased transcriptional activity, phosphorylation and methylation of DNA-histone complexes, influence on the expression of various oncogenes (*c-myc, c-myb, c-ras*), and reduction of urokinase activity [8]. In addition neoplastic and normal colonocytes share different metabolic profiles. Colon cancer cells *in vivo* switch from a principally aerobic to an anaerobic metabolism, leading to incomplete butyrate oxidation and subsequent accumulation of butyrate or metabolic intermediates as well as pH changes. This, in turn, may enhance or inhibit gene expression when compared to normal cells. An alternative explanation might be that mutated proteins in the neoplastic colonocyte may have an altered specific affinity for butyrate, thus influencing signalling pathways [6].

Regarding colonic motility, SCFA either stimulate or inhibit colonic contractions. Thus, they may serve to regulate the overall transit through the large intestine, control colonic absorption and, finally, may represent a self-regulating mechanism for fermentation [34].

Postulated effective dosage and possible side effects

The proliferation promoting effect of SCFA on human colonic biopsies can be observed in physiological concentrations. A combination of the three major SCFA (acetate 60 mM, propionate 25 mM, butyrate 10 mM) doubled the number of colonocytes in the S-phase of the cell cycle. As mentioned above, this enhanced proliferation occurs only in the basal crypt compartments, the physiological proliferation zone [9].

The antiproliferative effect of butyrate on neoplastic colonocytes *in vitro* can be observed at concentrations between 1 and 5 mmol/l without impairing cell viability, which is below the physiological concentration in the colon [37, 38]. At higher levels cytotoxic effects occur. In contrast with these findings, normal colonic tissue tolerates butyrate concentrations of 10–60 mmol/l [35]. This low effective dose is probably due to a higher susceptibility of isolated cells *in vitro* compared to tissue-associated cells in a natural environment. In a rat model of experimental colitis, butyrate enemas (80 mmol/l twice daily for 8 weeks) reduced incidence and size of tumors in the distal colon, affected colonic proliferation pattern and restored transglutaminase activity [39].

One problem in the administration of butyrate is its short metabolic half life. The intravenous infusion of sodium butyrate at 500 mg/kg body weight per day for several days in a child with leukemia resulted in only a short-lived remission due to the short metabolic half-life of butyrate of about 6 min and peak blood levels below 0.05 mM [40]. Higher rates of intravenous infusion could not be considered because of the risk of toxicity from sodium overload. This could be circumvented by the use of arginine salt, permitting the administration of higher doses and rates of infusion, but the low plasma levels and rapid metabolism remained unchanged [18]. In order to achieve the desired differentiation effects on cancer cells butyrate levels must be continuously elevated. In addition, possible interactions between butyrate and other nutrients need to be considered. However, in patients with ulcerative colitis, treatment with enema containing 100 mmol/l butyrate or a mixture of SCFA (acetate 60 mmol/l, propionate 30 mmol/l, butyrate 40 mmol/l) significantly decreased the proliferation rate in the upper crypt zones [41–43]. Additionally, an increase in colonic mucin synthesis could be observed in tissue from colonic resection samples after butyrate was added to standard nutrient medium, probably contributing to the therapeutic effect of butyrate in colitis [44].

Most current systemic approaches to achieve effective levels of butyrate in humans is the administration of tributyrin. Tributyrin is a SCT and a candidate precursor for butyrate that could be administered orally. The use of triglycerides reduces the problem of tissue irritation and toxicity that are produced by ingestion of large amounts of ionized free fatty acids together with large quantities of damaging cations such as sodium. Furthermore, SCFA in their respective triglyceride form provide a concentrated caloric delivery [20]. And finally, 1 mol of tributyrin supplies 3 mol of butyrate. In animal studies, plasma levels of 0.34 mmol could be achieved, and plasma half-life of butyrate following tributyrin administration was 40 min [18].

Studies to assess safety and tolerance of structured lipids revealed that they were well tolerated and appeared to be safe [21]. One study could show that plasma butyrate concentrations approaching 0.5 mM, the minimum effective *in vitro* concentration, could be achieved in patients after oral administration of tributyrin (50 to 400 mg/kg/day once daily for 3 weeks), without severe toxicity. However, the half-life of butyrate in plasma is extremely short, as peak plasma butyrate concentrations occurred between 0.25 and 3 h after application and disappeared from plasma by 5 h after the dose [45]. It is highly unlikely that once-daily administration of tributyrin will be sufficient to assess clinical activity. However, these data are most promising. For future research it will be necessary to further increase dosage and frequency of tributyrin administration to achieve higher plasma concentrations and to maintain the levels for a longer period.

Conclusion: the postulated beneficial effects of butyrate for the critically ill

Metabolism of SCFA, mainly butyrate, is crucial to the metabolic welfare of intestinal epithelium. There is an increasing body of evidence that endogenous starvation of colonocytes may be the cause of ulcerative colitis and other inflammatory conditions of the distal alimentary tract, possibly related to sulphide inactivation of fatty-acid dehydrogenases or inactivation of butyryl-CoA synthetase. Diminished fatty-acid oxidation would lead to a breached barrier of colonic epithelial cells and subsequent immune changes [2, 7].

The provision of appropriate cellular nutrients is particularly important to improve wound healing in intestinal surgery, support collagen synthesis, enhance epithelial proliferation and differentiation, and improve absorptive function [5]. Furthermore, one of the goals in clinical nutrition is to prevent or limit atrophy of the gastrointestinal tract and maintain the function of the gut mucosal barrier [20]. Clinical trials performed to test the benefit of SCFA, especially butyrate, on intestinal epithelium are encouraging and clearly point to a beneficial effect of these substances for critical ill patients. Butyrate, and also to a lesser degree propionate, are essential substrates for intestinal energy metabolism, and trophic factors of the mucosa. SCFA may promote the sealing of epithelial breaches, which restores barrier function and sets up a microenvironment more amenable to an efficient regenerative response [4]. SCFA enemas increase mucosal generation, crypt length, and DNA content of the colonocytes [46]. They also ameliorate symptoms of ulcerative colitis in human patients and, due to their differentiation-inducing effect in neoplastic cells, are protective in colon carcinogenesis.

Besides a diet rich in fibre, which increases the butyrate concentration in the intestine, the application of structured lipids like tributyrin are new promising targets for future research. They are excellent alternative sources of SCFA, yield a higher butyrate outcome, provide a concentrated source of calories, maintain intestinal function and support epithelial repair without increasing osmolarity of enteral formulas as do the free or salt form of SCFA [20, 21]. Additionally, most therapies are likely to require a prolonged duration, making i. v. administration costly and less attractive.

In spite of SCT being generally well tolerated, further work is needed to assess the risks and benefits of utilising tributyrin in nutrition regimens. The combination of differentiation agents with differing mechanisms may act synergistically to ameliorate the results. However, possible interactions of butyrate with other nutrients in the gut have not yet been fully elucidated and need to be considered. Therefore, the aim of future studies should be to determine the importance of SCFA in the therapy of a number of intestinal diseases and to pursue optimal use and dose required for metabolic efficacy of butyrate or oral agents such as tributyrin without toxic side-effects.

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