Abstract

The multiple beneficial effects on human health of the short-chain fatty acid butyrate, synthesized from non-absorbed carbohydrate by colonic microbiota, are well documented. At the intestinal level, butyrate plays a regulatory role on the transepithelial fluid transport, ameliorates mucosal inflammation and oxidative status, reinforces the epithelial defense barrier, and modulates visceral sensitivity and intestinal motility. In addition, a growing number of studies have stressed the role of butyrate in the prevention and inhibition of colorectal cancer. At the extraintestinal level, butyrate exerts potentially useful effects on many conditions, including hemoglobinopathies, genetic metabolic diseases, hypercholesterolemia, insulin resistance, and ischemic stroke. The mechanisms of action of butyrate are different; many of these are related to its potent regulatory effects on gene expression. These data suggest a wide spectrum of positive effects exerted by butyrate, with a high potential for a therapeutic use in human medicine.

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the luminal pH in the proximal colon is lower. This pH seems to boost the formation of butyrate, as mildly acidic pH values allow butyrate-producing bacteria to compete against Gram-negative carbohydrate-utilizing bacteria, such as Bacteroides spp. The ability to produce butyrate is widely distributed among the Gram-positive anaerobic bacteria that inhabit the human colon. Butyrate-producing bacteria represent a functional group, rather than a coherent phylogenetic group. Numerically, two of the most important groups of butyrate producers appear to be Faecalibacterium prausnitzii, which belongs to the Clostridium leptum (or clostridial cluster IV) cluster, and Eubacterium rectale/Roseburia spp., which belong to the Clostridium cocoides (or clostridial cluster XIVa) cluster of firmicute bacteria. Butyrate is the major energy source for colonocytes and is involved in the maintenance of colonic mucosal health. Recently several intestinal and extraintestinal effects of butyrate have been demonstrated (Figure 1 and Table 1). This review is focused on new evidence for possible applications of butyrate in human medicine.

**EFFECTS OF BUTYRATE AT THE INTESTINAL LEVEL**

**Effects on transepithelial ion transport**

Potentially, SCFAs are absorbed by each intestinal segment, as demonstrated in animal models and human volunteers. The colonocytes absorb butyrate and other SCFAs through different mechanisms of apical membrane SCFA uptake, including non-ionic diffusion, SCFA/HCO₃⁻ exchange, and active transport by SCFA transporters. The transport proteins involved are monocarboxylate transporter isofrom 1 (MCT1), which is coupled to a transmembrane H⁺-gradient, and SLC5A8, which is Na⁺-coupled co-transporter [15,16]. The absorption of these fatty acids has a significant impact on the absorption of NaCl and on the electrolyte balance generally [17]. In particular, butyrate is able to exert a powerful pro-absorptive stimulus on intestinal NaCl transport and an anti-secretory effect towards Cl⁻ absorption of NaCl and on the electrolyte balance general. Butyrate is the major energy source for colonocytes and is involved in the maintenance of colonic mucosal health. Butyrate is the major energy source for colonocytes and is involved in the maintenance of colonic mucosal health. Recently several intestinal and extraintestinal effects of butyrate have been demonstrated (Figure 1 and Table 1). This review is focused on new evidence for possible applications of butyrate in human medicine.

Effects on transepithelial ion transport

The interaction between CFTR and these components is mediated by binding of the regulatory domain of CFTR to the sulfate transporter and anti sigma factor antagonist (STAS) domain of SLC26. The interaction is enhanced by phosphorylation of the regulatory domain by protein kinase A and is modulated by PDZ-binding scaffold proteins. An important consequence of this interaction is that SLC26 anion exchange activity is enhanced when CFTR is activated by phosphorylation. Moreover, the two genes regulate each other: the overexpression of SLC26A3 or -A6 causes upregulation of CFTR and vice versa. In patch-clamp experiments, protein kinase A-stimulated CFTR channel activity was six-fold higher in HEK293 cells co-expressing both SCL26 anion exchanger and CFTR than in HEK293 cells expressing CFTR alone. Mutations may impair the interactions between channels and thus reduce the effect of butyrate therapy. Interestingly, it has been demonstrated that butyrate can act by different mechanisms in in vitro models of cystic fibrosis: it can increase the expression of the apical epithelial membrane of the CFTR, and it can act as a "chaperone-like" molecule, as shown in the ΔF508del CFTR cell line model. Similar mechanisms could occur in IBD. Lastly, Clausen et al demonstrated that antibiotic-associated diarrhea was related to reduced fecal concentrations and production rates of butyrate. Their results suggest that
the antibiotic-associated diarrhea might be secondary to impaired colonic fermentation in otherwise disposed subjects, resulting in decreased butyrate and fluid absorption. In this case, the administration of butyrate could also alleviate the symptoms associated with antibiotic use.

**Effects on cell growth and differentiation**

Several epidemiological studies support the role of dietary fiber in the protection against colorectal cancer. Different mechanisms have been proposed for fiber's cancer preventive properties: reduction in transit time of the feces in the gut, which reduces exposure of the mucosa to luminal carcinogens; absorption of bile acids, biogenic amines, bacterial toxins, and production of butyrate. Most of the anticarcinogenic effects of butyrate are observed in *in vitro* carcinoma cell lines. In these models, addition of butyrate leads to inhibition of proliferation, induction of apoptosis, or differentiation of tumor cells. Butyrate's anticarcinogenic effects are in contrast with the effects of this compound in normal enterocytes. In fact, it has been shown that butyrate stimulates the physiological pattern of proliferation in the basal crypt in the colon, whereas it reduces the number and the size of aberrant crypt focus, which are the earliest detectable neoplastic lesions in the colon. These contradictory patterns of butyrate represent the so-called "butyrate paradox." An important mechanism by which butyrate causes biological effects in colon carcinoma cells is the hyperacetylation of histones by inhibiting histone deacetylase (HDAC). This compensates for an imbalance of histone acetylation, which can lead to transcriptional dysregulation and silencing of genes that are involved in the control of cell cycle progression, differentiation, apoptosis and cancer development. In particular, in human colon cancer cell lines butyrate, acting as HDAC inhibitor, increases the p21 (WAF1) gene expression by selectively regulating the degree of acetylation of the gene-associated histones, and induces G1 cell cycle arrest. A novel contributory mechanism to the chemopreventive effect of butyrate is the downregulation of the key apoptotic and angiogenesis regulator Neuropilin-1 (NRP-1), which has been shown to promote tumor cell migration and survival in colon cancer in response to vascular endothelial growth factor (VEGF) binding. Several reports have shown that the apoptosis triggered by butyrate *in vitro* is associated with dysregulation of Bcl2 family proteins, especially upregulation of BAK and downregulation of BclxL, rather than cellular damage. A study by Thangaraju *et al* suggests a novel mode of action of butyrate in the colon involving GPR109A, a G-protein–coupled receptor for nicotinate, which recognizes butyrate with low affinity. This receptor is expressed in the normal colon on the luminal facing apical membrane of colonic epithelial cells, but is silenced in colon cancer *via* DNA methylation. Thangaraju *et al* showed that inhibition of DNA methylation in colon cancer cells induces GPR109A expression and that activation of the receptor causes tumor cell–specific apoptosis. Butyrate is an inhibitor of HDAC, but apoptosis induced by activation of GPR109A with its ligands in colon cancer cells does not involve inhibition of histone deacetylation. The primary changes in this apoptotic pro-

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**Table 1** Main butyrate effects potentially useful in human medicine

<table>
<thead>
<tr>
<th>Intestinal level</th>
<th>Extraintestinal level</th>
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<tbody>
<tr>
<td>Ion absorption</td>
<td>Insulin sensitivity</td>
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<tr>
<td>Cell proliferation</td>
<td>Cholesterol synthesis</td>
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<tr>
<td>Cell differentiation</td>
<td>Energy expenditure</td>
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<tr>
<td>Intestinal barrier function</td>
<td>Ammonia scavenger</td>
</tr>
<tr>
<td>Immune-regulation</td>
<td>Stimulation of β-oxidation of very long chain fatty acids and peroxisome proliferation</td>
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<tr>
<td>Oxidative stress</td>
<td>CFTR function</td>
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<tr>
<td>Intestinal motility</td>
<td>Neurogenesis</td>
</tr>
<tr>
<td>Visceral perception and rectal compliance</td>
<td>HbF production</td>
</tr>
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CFTR: Cystic fibrosis transmembrane conductance regulator; HbF: Butyrate to increase fetal hemoglobin.

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Figure 1 The multiple effects of butyrate at intestinal level.
cess include downregulation of Bel-2, Bcl-xL, and cyclin D1 and upregulation of death receptor pathway. Moreover, a recent study suggested that the protective role of dietary fiber, and its breakdown product butyrate, against colorectal cancer could be determined by a modulation of canonical Wnt signaling, a pathway constitutively activated in the majority of colorectal cancers [43]. Butyrate is recognized for its potential to act on secondary chemoprevention, by slowing growth and activating apoptosis in colon cancer cells [44], but it can also act on primary chemoprevention. The mechanism proposed is the transcriptional upregulation of detoxifying enzymes, such as glutathione-S-transferases (GSTs). This modulation of genes may protect cells from genotoxic carcinogens, such as H2O2 and 4-hydroxynonenal (HNE) [45,46].

**Effects on inflammatory and oxidative status**

Butyrate has a role as an anti-inflammatory agent, primarily via inhibition of nuclear factor κB (NF-κB) activation in human colonic epithelial cells [47], which may result from the inhibition of HDAC. NF-κB regulates many cellular genes involved in early immune inflammatory responses, including IL-1b, TNF-α, IL-2, IL-6, IL-8, IL-12, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), intercellular adhesion molecule-1 (ICAM-1), vascular cellular adhesion molecule-1 (VCAM-1), T cell receptor-α (TCR-α), and MHC class II molecules [48-50]. The activity of NF-κB is frequently dysregulated in colon cancer [51,52] and in inflammatory bowel diseases (IBDs), such as ulcerative colitis (UC) and Crohn's disease (CD) [53-55]. In CD patients, butyrate decreases pro-inflammatory cytokine expression via inhibition of NF-κB activation and IkBα degradation [48]. The upregulation of peroxisome proliferator-activated receptor γ (PPARγ) a nuclear receptor highly expressed in colonic epithelial cells, and the inhibition of IFNγ signaling, are another two of butyrate’s anti-inflammatory effects [56-58]. Butyrate can act on immune cells through specific G-protein-coupled receptors (GPRs) for SCFAs, GPR41 (or FFA3) and GPR43 (or FFA2), which are both expressed on immune cells, including polymorphonuclear cells, suggesting that butyrate might be involved in the activation of leukocyte [59]. The possible immune-modulatory functions of SCFAs are highlighted by a recent study on GPR43 -/- mice. These mice exhibit aggravated inflammation, related to increased production of inflammatory mediators and increased immune cell recruitment [59].

Most clinical studies analyzing the effects of butyrate on inflammatory status focused on UC patients. Hallert et al. [60] instructed 22 patients with quiescent UC to add 60 g oat bran (corresponding to 20 g dietary fiber) to their daily diet. Four weeks of this treatment resulted in a significant increase of fecal butyrate concentration and in a significant improvement of abdominal symptoms. In a double blind, placebo-controlled multicenter trial, Vernia et al. [61] treated 51 patients with active distal UC with rectal enemas containing either 5-aminosalicylic acid (5-ASA) or 5-ASA plus sodium butyrate (80 mmol/L, twice a day). The combined treatment with topical 5-ASA plus sodium butyrate significantly improved the disease activity score more than 5-ASA alone. These and other intervention studies [62-64] suggested that the luminal administration of butyrate or stimulation of luminal butyrate production by the ingestion of dietary fiber results in an amelioration of the inflammation and symptoms in UC patients.

Numerous studies have reported that butyrate metabolism is impaired in intestinal inflamed mucosa of patients with IBD. Recent data show that butyrate deficiency results from the reduction of butyrate uptake by the inflamed mucosa through downregulation of MCT1. The concomitant induction of the glucose transporter GLUT1 suggests that inflammation could induce a metabolic switch from butyrate to glucose oxidation. Butyrate transport deficiency is expected to have clinical consequences. Particularly, the reduction of the intracellular availability of butyrate in colonicocytes may decrease its protective effects toward cancer in IBD patients [63].

Limited evidence from pre-clinical studies shows that oxidative stress in the colonic mucosa can be modulated by butyrate. Oxidative stress is involved in both inflammation [65] and the process of initiation and progression of carcinogenesis [66]. During oxidative stress there is an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense mechanisms, leading to a cascade of reactions in which lipids, proteins, and/or DNA may get damaged. In healthy humans, it has been demonstrated that locally administered butyrate in physiological concentrations increased the antioxidant GSH and possibly decreased ROS production, as indicated by a decreased uric acid production [67]. As the human colon is continuously exposed to a variety of toxic stimuli, enhanced butyrate production in the colon could result in an enhanced resistance against toxic stimuli, thus improving the barrier function. This might be relevant for the treatment of gastrointestinal disorders, such as post-infectious irritable bowel syndrome (IBS), microscopic colitis, IBD, and diversion colitis.

**Effects on non-specific intestinal defense mechanisms**

The main components of nonspecific intestinal barrier defense mechanisms are the mucous layer covering the epithelium, the production of antimicrobial peptides, and tight junctions, which protect the gastrointestinal mucosa against pathogens. Evidence suggests a role for butyrate in reinforcing the colonic defense barrier. Butyrate stimulates MUC2 mucin production in a human colonicocytes cell line (LS174T). The increased expression of MUC2 gene, and the induction of mucin synthesis, can affect the mucous layer leading to enhanced protection against luminal agents [66,67].

Combined with other components of the innate immune system, antimicrobial peptides (AMPs) form the first line of defense against infections. The two major
classes of AMPs found in humans are defensins and cathelicidins. While the intestine expresses numerous defensins, LL-37 is the only cathelicidin-derived peptide expressed in humans. Several studies demonstrated an effect of butyrate on LL-37 gene expression and proposed that the molecular mechanism may be linked to an increase in histone acetylation and mitogen-activated protein (MAP) kinase signaling\cite{78,79,80}. The use of HDAC inhibitors, such as butyrate, to enhance the expression of the LL-37 gene may become a novel approach for strengthening innate immunity to treat or prevent intestinal infections.

Butyrate also regulates the colonic defense barrier through its effects on intestinal permeability, which depends on its concentration. At low concentrations, butyrate induces a concentration-dependent reversible decrease in permeability in intestinal cell line models\cite{81,82}. The effect of butyrate on the intestinal epithelial permeability involves the assembly of tight junctions via AMP-activated protein kinase (AMPK)\cite{83}.

**Effects on visceral perception and intestinal motility**

Little is known about the environmental and nutritional regulation of the enteric nervous system (ENS), which controls gastrointestinal motility. Butyrate regulates colonic mucosa homeostasis and can modulate neuronal excitability. Soret et al\cite{84} investigated the effects of butyrate on the ENS and colonic motility, and showed, \textit{in vivo} and \textit{in vitro}, that butyrate significantly increased the proportion of choline acetyltransferase (ChAT), but not nitric oxide synthase (nNOS) immunoreactive myenteric neurons. Butyrate increases the cholinergic-mediated colonic circular muscle contractile response \textit{ex vivo}. The authors suggest that butyrate might be used, along with nutritional approaches, to treat various gastrointestinal motility disorders associated with inhibition of colonic transit.

A recent study by Van Houten \textit{et al}\cite{85} shows that intraluminal administration of a physiologically relevant dose (50 to 100 mmol/L) of butyrate into the distal colon increases compliance and decreases pain, urge, and discomfort measured with a rectal barostat procedure in healthy subjects. This study suggests a potential beneficial effect of butyrate in disorders that are associated with visceral hypersensitivity, such as IBS and infantile colics, and provides a basis for future trials with dietary approaches, to treat various gastrointestinal motility disorders associated with inhibition of colonic transit.

The possible use of butyrate in the treatment of X-linked Adrenoleukodystrophy (X-ALD), a disorder of peroxisomes characterized by altered metabolism and accumulation of very long chain fatty acids, has also been studied. Sodium phenylbutyrate 4 induces, \textit{in vitro} on fibroblasts from patients with X-ALD and \textit{in vivo} in X-ALD knockout mice, an increase in β-oxidation of very long chain fatty acids and peroxisome proliferation\cite{86}.

**Hypercholesterolemia**

Under normal lipidemic conditions, the liver is the most important site of cholesterol biosynthesis, followed by the intestine. Biosynthesis in the liver and intestine account for about 15% and 10%, respectively, of the total amount of cholesterol biosynthesis each day\cite{87,88}. In hypercholesterolemia, when cholesterol biosynthesis is suppressed in most organs by fasting, the intestine becomes the major site of cholesterol biosynthesis, and its contribution can increase up to 50%. Importantly, recent evidence shows that the global effect of butyrate is to downregulate the colonic circular muscle. The dose-dependent contractile effect occurred only when SCFAs were applied on the mucosal side and disappeared in mucosal free preparations, suggesting the presence of sensory mechanisms near the epithelium\cite{89,90}.

**EFFECTS AT THE EXTRAINTESTINAL LEVEL**

**Hemoglobinopathies**

Clinical trials in patients with sickle cell disease and β-thalassemia confirmed the ability of butyrate to increase fetal hemoglobin (HbF) production\cite{91,92,93}. Butyrate is an inducer of HbF through an epigenetic regulation of fetal globin gene expression \textit{via} HDAC inhibition, resulting in global histone hyperacetylation, including nucleosomes at the γ-globin promoters\cite{94}. Other experiments have shown that butyrate can cause a rapid increase in the association of γ-globin mRNA with ribosomes\cite{95}. Other authors have demonstrated activation of p38 mitogen-activated protein kinases (MAPK) and cyclic nucleotide signaling pathways in association with butyrate induction of HbF\cite{96}. Taken together, these studies suggest that global histone hyperacetylation induced by HDAC inhibition is not the unique mechanism underlying butyrate stimulation of HbF.

**Genetic metabolic diseases**

Sodium phenylbutyrate 4 (4-PBA) was approved by the Food and Drug Administration (FDA) for use in patients with urea cycle enzyme deficiency, in which it acts as a scavenger of ammonia. Indeed, 4-PBA is oxidized to phenylacetate, which binds to glutamine and determines the urinary excretion. In patients with ornithine transcarbamylase deficiency, the use of 4-PBA allows for better metabolic control and increased intake of natural protein in the diet\cite{97}.

The possible use of butyrate in the treatment of X-linked Adrenoleukodystrophy (X-ALD), a disorder of peroxisomes characterized by altered metabolism and accumulation of very long chain fatty acids, has also been studied. Sodium phenylbutyrate 4 induces, \textit{in vitro} on fibroblasts from patients with X-ALD and \textit{in vivo} in X-ALD knockout mice, an increase in β-oxidation of very long chain fatty acids and peroxisome proliferation\cite{98}.
expression of nine key genes involved in intestinal cholesterol biosynthesis, potentially inhibiting this pathway[97].

**Obesity and insulin resistance**

Dietary supplementation with butyrate can prevent and treat diet-induced obesity and insulin resistance in mouse models. After a 5-wk treatment with butyrate, obese mice lost 10.2% of their original body weight. Consistent with the change in body weight, fat content was reduced by 10%. Furthermore, fasting glucose was reduced by 30%, insulin resistance was reduced by 50%, and intraperitoneal insulin tolerance was improved significantly by butyrate. The mechanism of butyrate action is related to promotion of energy expenditure and induction of mitochondrial function. Stimulation of peroxisome proliferator-activated receptor (PPAR) coactivator (PGC-1α) activity has been suggested as the molecular mechanism of butyrate. Activation of AMPK and inhibition of histone deacetylases may contribute to the PGC-1α regulation. These data suggest that butyrate may have potential application in the prevention and treatment of metabolic syndrome in humans[98].

**Ischemic stroke**

Cerebral ischemia enhances neurogenesis in neurogenic and non-neurogenic regions of the ischemic brain of adult animal models. A recent study demonstrated that post-insult treatment with sodium butyrate stimulated the incorporation of bromo-2'-deoxyuridine (BrdU) in the ischemic brain of rats subjected to permanent cerebral ischemia. Butyrate treatment also increased the number of cells expressing polysialic acid-neural cell adhesion molecule, nestin, glial fibrillary acidic protein, phospho-CAMP response element-binding protein (CREB), and brain-derived neurotrophic factor (BDNF) in various brain regions after cerebral ischemia[99]. Furthermore, extensive co-localization of BrdU and polysialic acid-neural cell adhesion molecule was observed in multiple regions after ischemia, and butyrate treatment upregulated protein levels of BDNF, phospho-CREB, and glial fibrillary acidic protein. Intraventricular injection of K252a, a tyrosine kinase B receptor antagonist, markedly reduced the long-lasting behavioral benefits of butyrate, inhibiting cell proliferation, nestin expression, and CREB activation[100]. Together, these results suggest that butyrate-induced cell proliferation, migration, and differentiation require BDNF-tyrosine kinase B signaling and may contribute to long-term beneficial effects of butyrate after ischemic injury.

**ISSUES RELATED TO THE CLINICAL USE OF BUTYRATE**

Data from literature and clinical experience of several research groups show a wide spectrum of possibilities for potential therapeutic use of butyrate by oral administration without having serious adverse events (Table 2). Some butyrate-based products are marketed, but their spread is still very limited and greatly understaffed in view of the wide spectrum of possible indications, especially in chronic diseases, where it is possible to predict a lasting use of the compound. The main problem is of the availability of formulations of butyrate that can be easily administered orally, in particular for pediatric patients, and to the extremely poor palatability of the products available on the market. The unpleasant taste and odor make oral administration of butyrate extremely difficult, especially in children. Thus, new formulations of butyrate with a better palatability, which can be easily administered orally, are needed. Another possible solution could be the modulation of intestinal microflora by probiotics. Probiotics are live and viable microorganisms, which, if given in adequate amounts, confer a beneficial effect to the host. Probiotic microorganisms generate small molecular metabolic byproducts, referred to as “postbiotics”, which exert beneficial regulatory influence on host biological functions, including butyrate[101].

**CONCLUSION**

The SCFA butyrate, a main end product of microbial fermentation of dietary fibers in the human intestine,
plays an important role in the maintenance of intestinal homeostasis and overall health status. The effects exerted by butyrate are multiple and involve several distinct mechanisms of action. Its well-known epigenetic mechanism, through the inhibition of HDACs, results in the regulation of gene expression and in the control of cell fate. At the intestinal level, butyrate exerts multiple effects such as the prevention and inhibition of colonic carcinogenesis, the improvement of inflammation, oxidative status, epithelial defense barrier, and the modulation of visceral sensitivity and intestinal motorility. At the extraintestinal level, potential fields of application for butyrate seem to be the treatment of sickle cell disease, β-thalassemia, cystic fibrosis, urea cycle enzyme deficiency, X-linked adrenoleukodystrophy, hypercholesterolemia, obesity, insulin resistance, and ischemic stroke.

In conclusion, a growing number of studies have revealed new mechanisms and effects of butyrate with a wide range of potential clinical applications from the intestinal tract to peripheral tissues. However, more clinical studies to elucidate the role of butyrate in health and diseases and new solutions for easier administration are needed.

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