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Original Article

Anti-inflammatory activity of butyrate: therapeutic effects, educative strategies and potential implications for an athlete's health

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Abstract:
Short chain fatty acid butyrate is a compound physiologically produced in human colon by resident flora fermentation of undigested carbohydrates. The multiple beneficial effects of butyrate on human health are well documented. Butyrate is able to modulate a wide range of processes like the ion transport, the maintenance of the intestinal barrier, the mucosa trophism and metabolism, the visceral perception and the intestinal motility. Some of these effects depend on the inhibition that butyrate exerts on the enzyme hystone deacetylase that in turn modulates gene expression for hundreds of genes. The global level of hystone acetylation is relevant for many common diseases including inflammation related diseases like obesity, diabetes mellitus, neurodegenerative diseases and cancer, as well as for some rare diseases such as mitochondrial diseases and lipodystrophies. Although butyrate represents a minor intermediate of fiber digestion, many evidences demonstrate that it has the stronger anti-inflammatory action among SCFAs. Here we focus on known targets and anti-inflammatory mechanisms of butyrate action and discuss the latest anti-inflammatory therapeutic strategies related to the use of this compound in human diseases. We also investigate about exercise effect on gut microbioma.
Key words: SCFA, butyrate, HDAC inhibitor, HAT activator, inflammation, physical activity, exercise.

Introduction

Butyrate is an organic acid principally produced by intestinal microbial fermentation of undigested carbohydrates and, only in minor part, by dietary and endogenous proteins (1). It belongs to the Short Chain Fatty Acids (SCFAs) family that includes acetate (C2), propionate (C3), butyrate (C4), and valerate (C5), which are essentially produced in the large intestine of mammalians. SCFAs concentrations are maximal in proximal colon, reaching 70-140 mM, and declines toward the distal colon (20-70 mM) (2). In humans, butyrate production is influenced by multiple factors as microbiota composition, pH of intestinal lumen, nutrients intake, dietary habits, gut transit time, etc. Phylogenetic related groups of Gram-positive anaerobic bacteria that inhabit the human colon constitute the major source of endogenous butyrate. Numerically, the two most important groups of butyrate producers are *Faecalibuacterium prausnitzii*, which belongs to the *Clostridium leptum* (or clostridial cluster IV) cluster, and *Eubacterium rectale/Roseburia spp*, which belong to the *Clostridium coccoides* (or clostridial cluster XIVa), a cluster of firmicute bacteria (3). It's well documented that the type of fibers has an important impact on microbial composition (4). Examples of SCFAs sources are oligosaccharides like raffinose, oligofructose, inulin and not soluble carbohydrates like cellulose and hemicellulose. The most important substrate for butyrate production seems to be the resistant starch (D-glucose units connected by α-1,4/α-1,6, glycosidic bonds). Resistant starch (RS) can be subdivided into four type: physically trapped starch (in coarse grains), granules rich in amylose (i.e. raw potato flour), retrograded starch (cooked and cooled potato) and chemically modified starch (i.e. processed foods) (5). Several *in vitro* and *in vivo* studies demonstrated that resistant starch fermentation generates relatively more butyrate than other carbohydrates (6). SCFAs production from undigested carbohydrates is articulated in different steps: first, the undigested carbohydrates are broken down into monosaccharides via microbial hydrolysis. Secondly, the monosaccharides are fermented to phosphoenolpyruvate via the Embden-Meyerhof-Parnas pathway. Finally, acetate, propionate and butyrate are produced from phosphoenolpyruvate via different reactions. In particular, the production of acetate and butyrate requires phosphoenolpyruvate convertion into acetyl-coenzyme A. In many firmicutes, acetate is formed directly from acetyl-CoA. Instead, butyrate can be produced only in presence of acetate via either butyrate kinase or butyryl-CoA acetate CoA transferase. Among SCFAs, acetate is the most representative and covers about the 60% of total products of bacteria fermentation, propionate 25% and butyrate only 15%. SCFAs are metabolized by colon epithelial cells to which they constitute approximately 60-70% of the energy requirement. The hierarchy of utilization of SCFAs by colonocytes in physiological conditions is butyrate>propionate>acetate (7). However, this hierarchy reflects several factors including the diet influence. In healthy adults with a westernized diet, acetate is the main energy source for colon and the molar ratios of butyrate to propionate to acetate,

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calculated on the basis of fecal measurement, are approximately 20:20:60 (8). After production in the colon, SCFAs are rapidly absorbed and used by colon epithelium. Only a few part (from 5% to 10%) is excreted in feces, while the remaining part is transported through the portal vein to the liver (9). Although butyrate represents a minor intermediate of fiber digestion, many evidences demonstrate that it has the stronger anti-inflammatory action among SCFAs (10; 11). The SCFAs that are not metabolized by colon epithelium reach systemic circulation both by passive diffusion and by proton-coupled monocarboxylate transporters (MCTs) and sodium-coupled MCTs (SMCTs) which are expressed in different organs and tissues like gastro intestinal tract, liver, pancreas, heart, brain and skeletal muscle (12). MCTs and SMCTs differential tissue expression may explain the systemic effect of SCFA molecules produced at intestinal level. Several authors described the positive relation between high level of fibers consumption and blood concentrations of butyrate in preventing inflammation related pathologies as type 2 diabetes, cardiovascular disease and obesity (13; 14). Experiments in rodents show that butyrate generated from dietary fiber fermentation at a high dose in the hindgut lumen (from 3 to 70 mM) is quickly absorbed and transported via the portal vein to the liver (15). In humans it has been demonstrated that butyrate can reach concentrations of 30μM in the portal vein and of 12 μM in the hepatic vein (16). However, data about butyrate concentration in peripheral blood are discordant: Cummings et al. failed to detect blood butyrate concentration in samples obtained at autopsy of sudden death victims with British diet (17). Again in humans, Nillson et al. found that plasma concentrations of butyrate in the morning were affected by food consumed in the previous evening and in breakfast. In volunteers, plasma butyrate and propionate concentrations increase 30 min after a standardized breakfast with 50g of available starch, reaching concentrations of 2.7 ± 0.11 μmol/L and 8.0 ± 0.17 μmol/L respectively (18). A recent study reported that butyrate concentration in radial vein measured 5 minute after a butyrate enema is approximately 1.1 ± 0.4 μmol/L, suggesting the high capacity of liver of metabolizing rectally administered butyrate rapidly, determining low circulating butyrate concentrations (19). However, no data are present in literature about plasma concentration of butyrate in subjects with a high fiber diet, like vegetarians, in which fiber content may reach 60g/day, while it was estimated that the average human diet in western societies contains approximately 20-25g fiber/day (20). Butyrate exerts multiple functions useful for the maintenance of healthy status both at intestinal and extra intestinal levels. This compound is involved in the maintenance of colonic mucosal health and in cellular differentiation. The anti-cancer effect of butyrate is determined by apoptosis induction of transformed colonocytes. It is known that butyrate acts as inhibitor of the enzyme hystone deacetylase and its modulation of gene expression was reported for more than one hundred genes. Several studies focused on butyrate ability of degreasing the transformation of primary to secondary bile acids as a result of colonic acidification (21-23). In the last years promising therapies based on butyrate administration are proposed with the scope to exploit the butyrate ability of modulating acute and chronic inflammation both at gastrointestinal level and extra intestinal level. This review focuses on known targets and anti-inflammatory mechanisms of butyrate action. Here, we also discuss the latest anti-inflammatory therapeutic strategies related to the use of this compound in human medicine.

Absorption, transport and metabolism of butyrate

Butyrate absorption in gut is regulated by differentially expressed transporters from the small to the large intestine (24). On the apical membrane of enterocytes, butyrate transport is realized by passive diffusion of unionized form and other mechanisms involving SCFA/HCO^{3-} exchangers, H^+-coupled MonoCarboxylate Transporters (MTC) (25) and Sodium-coupled MonoCarboxylate Transporters (SMTC or SLCA8 and 12) (26) for ionized form involving co-transport of inorganic protons like Na^+, K^+ and H^+. MCT-1 was the first SCFAs transporter identified and localized in other extraintesinal tissues like heart, kidney and epididymis (27). In human colonic mucosa, a low expression for MTC3 was detected in ileum while a high expression of MTC4 and MTC5 was detected in distal colon. Butyrate transport mediated by MCTs is saturable, pH dependent and inhibited by several other monocarboxylates. The second class of MCT, named SMCT, coupled Na^+ uptake to butyrate internalization, but it is also capable to use nicotinate and ketone bodies as substrate. The two SMCT members identified, SLC5A8 (SMCT1) and SLC5A12 (SMCT2), were found to be expressed not only in the gastrointestinal tract but also in kidney, thyroid, brain, and retina. SLC5A8 and SLC5A12 are considered tumor suppressors, in fact SLC5A8 is silenced via hypermethylation during malignant transformation of human colon (28). SLC5A8 expression, restored by *in vitro* butyrate treatment, is able to induce colon cancer cell apoptosis, probably mediated by reactivation of butyrate internalization and deacetylase inhibition (29). Similarly, SLC5A12 seems to act as tumor suppressor because it was found to be expressed in non transformed cells and not expressed in malignant cells (30). SLC5A8 can also transport a variety of pharmacologically relevant monocarboxylates, including salicylates, benzoate, and γ-hydroxybutyrate. Non-steroidal anti-inflammatory drugs such as ibuprofen, ketoprofen, and fenoprofen interact with SLC5A8 acting as transporters blockers. Relatively less is known about the role of SLC5A12 in drug transport. The basolateral membrane movement of butyrate is regulated by a HCO^{3-} gradient dependent anion butyrate exchange system both in ileum and in colon identified by Tyagi et al. in 2002, who characterized a pH-sensitive anion butyrate exchanger in colonic basolateral membrane vescicles (31). Kinetic analysis and trans stimulation experiments confirmed that butyrate transport across basolateral membrane is driven by two distinct electroneutral Cl^-/HCO^{-3}(32) and

SCFA/HCO^{-3}(33) exchangers in the human proximal colon, however the identity of these exchangers still remains unknown. In addition, in 2003, two intestinal orphan G protein-coupled receptors (GPRs) GPR41 (or *FFA3*) and GPR43 (or *FFA2*) were identified as SCFAs responsive receptors. Later, other SCFAs receptors belonging to the same subfamily were identified. GPR43 mRNA, also called Free Fatty Acid receptor 2 (FFA2), was detected in a variety of tissues, including immune cells. The highest expression was found in polymorphonuclear cells, suggesting that SCFA might be involved in the activation of leucocytes. FFA3 has an even more widespread expression pattern than FFA2, including adipose tissues, pancreas, spleen, lymph nodes, bone marrow and peripheral blood mononuclear cells (34). In 2013, Arpaia et al. demonstrated that butyrate facilitates extrathymic generation of regulatory T (Treg) and dentritic cells differentiation in mice via GPRs activation. The interaction between butyrate and its receptor led to a cascade signal that culminates with transcription factor Foxp3 expression. In literature it was reported that Foxp3 plays a key role limiting inflammatory responses in intestine (35). GPR43-deficient *(Gpr43$^{-/-}$)* mice showed exacerbated or unresolved inflammation in models of colitis, arthritis and asthma. This relates to the increased production of inflammatory mediators by *Gpr43$^{-/-}$*immune cells and increased immune cell recruitment. In liver, white and brown adipose tissues and muscles, SFCAs act as regulators of fatty acid metabolism. This effect is well characterized in white adipose tissue where FFA2 receptor seems to increase leptin release into the blood and insulin sensitivity by AMP-activated protein kinase (AMPK) pathway and cAMP intracellular accumulation. AMPK activity is positively regulated by SFCAs also in muscle and liver (36). In human intestine, a sub population of enteroendocrine cells shows a positive double immunostaining for FFA2 and FFA3 and a contemporary immunoreactive positivity for peptide YY, suggesting the link between SCFAs and physiological processes like intestinal motility, secretion, innate immunity, satiety, etc (37). In 2007, OAT7/SLC22A9 was identified as the first liver-specific transporter among members of the organic anion transporters of SLC22 family that transports anionic substances such as sulfate-conjugates in exchange for butyrate in hepatocytes (38). In colonocytes, butyrate metabolism is responsible of approximately 70% of intracellular ATP production (39) being oxidized into CO_2 via fatty acids oxidation in mitochondria. It can be used also as precursor for lipid synthesis, increasing lipogenesis from ketone bodies or acetyl-CoA (40). Actually, germ-free mice, which are devoid of bacteria and product little or no SCFAs, provide a functional model useful to investigate molecular link between diet, gastrointestinal bacterial metabolism and immune and inflammatory responses. In 2011, Donohoe et al. observed that colonocytes from germfree mice show an energy-deprived state and exhibit decreased expression of enzymes that catalyze key steps in intermediary metabolism including the tricarboxylic acid cycle. Consequently, a marked decrease in NADH/NAD+ was observed together with a reduction of ATP levels, which resulted in AMPK activation and autophagy via p27kip1 phosphorylation. Authors also observed that butyrate added to germfree colonocytes is able to rescue their deficit in mitochondrial respiration and to prevent them from autophagy due to fact that butyrate acts as an energy source rather than as an Histone Deacetylase inhibitor (HDAC) (41). It is known that transformed cells undergo to a metabolic shift characterized by preferential utilization of aerobic glycolysis instead of oxidative metabolism. This condition, known as Warburg effect (42), is associated with an altered production and utilization of numerous metabolites including acetyl-CoA. Acetyl-CoA is not only involved in cellular metabolism but it acts also as essential co-factor for histone acetyl transferases (HATs) that epigenetically regulate gene expression (43). HAT and HDAC enzymatic activities were found systematically perturbed in most type of cancers. In 2012, Donohoe et al. demonstrated that a concentration of 5 mM of sodium butyrate (NaB) is able to explicate the previously reported HDAC inhibition, mediated by intracellular accumulation of butyrate on HCT116 colon carcinoma cells nucleus, but a dose of 0,5 mM of NaB is able to increase the global histone acetylation levels by an alternative mechanism distinct from its role as HDAC inhibitor and characterized by increasing HATs enzyme activity. Authors concluded that, at low doses, butyrate may exert its stimulatory effect not only by serving as a carbon source for β-oxidation and for Tricarbossilic TCA cycle but also by increasing acetyl-CoA production for lipid biosynthesis and/or acetylation of lysine residues via nuclear ATP citrate lyase (ACL). Recently, ACL, the cytosolic key enzyme for acetyl-CoA synthesis, was richly found in nucleus were regulates histone acetylation in response to growth factor stimulations and during differentiation, representing a link between growth-factor-induced increases in nutrient metabolism and gene expression in mammalians (44). In this model, butyrate should function both as an acetyl-CoA donor and HAT activity stimulator in an ACL-dependent manner (45). A 5 mM dose of butyrate in vitro reflects the physiological production detected in the colon lumen (46-48). However, some authors supposed the presence of gradient of exposure to butyrate in human colon lumen which is maximal at the top of the crypts and decrease progressively at the crypt bases (48,49). The gradient is generated by the thick layer of mucous (~100 mm) produced by goblet cells and flows up from the crypt bases into the lumen and down the lumen due to peristalsis. Therefore, if butyrate production is approximately from 3 to 70 mM in hindgut lumen (15), only a small number of butyrate molecules reaches the basis of the crypts in vivo (~50-800 μM dose equivalent) causing the acetyl-CoA/HAT activation mechanism rather than HDAC-inhibition, a mechanism most utilized by the enterocytes chronically exposed to high butyrate levels. This hypothesis is partially confirmed by butyrate measurements performed in the lumen of mouse colon by liquid chromatography tandem mass spectrometry (LC-MS/MS), detecting concentrations of 3.5mM, 0.8mM and 0.5mM in the proximal, medial and distal segments, respectively, and a range of concentration between 50 and 800 μM in the colonic crypts (50). These

findings might explain why butyrate facilitates the normal turnover of the colonic epithelium by promoting colonocyte proliferation in the bottom half of each crypt while increasing apoptosis in those cells that exfoliate into the lumen.

Butyrate targets and butyrate effects on inflammatory and oxidative status

Chronic inflammatory disorders like Ulcerative Colitis (UC) and Crohn's disease (CD) are immune disorders affecting the gastrointestinal tract, also denominated inflammatory bowel diseases (IBD). IBD etiology is still poor understood, but emerging evidences suggest that the imbalance between microbiota and host response may constitute a trigger for the establishment of chronic inflammation (51). Among SCFAs, several studies reported the strongest butyrate ability to modulate inflammation in different cell types. In 2015, Iraporda et al. reported that a concentration of 1 to 5 mM of butyrate inhibits interleukins IL6 and IL12p40 lipopolysaccharide (LPS) induced secretion by myeloid cells in a dose dependent manner (52). In the same study, butyrate and propionate shown higher capacity than other SCFAs to modulate inflammatory activation of intestinal epithelial cells without citotoxicity or mitochondrial activity perturbation of treated cells.

Several evidences suggest that the main anti-inflammatory effect of butyrate is related to the inhibition of nuclear factor κB (NF-κB) activation in human colonic epithelial cells promoted by inhibition of IκB-degradation. IκB-α is an inhibitor of NF-κB that prevents its nuclear translocation and its degradation is correlated with butyrate inhibition of HDAC (53). The chronic inflammation in IBD is characterized by activation pro-inflammatory cytokines like interleukins (IL) and tumor necrosis factor-alpha (TNF-α). NF-kB regulates many genes involved in innate immunity, cell cycle control, apoptosis, early and chronic inflammatory responses, including IL-1β, TNF-α, IL-2, IL-6, IL-8, IL-12, inducible nitric oxide synthase (iNOS), cycloxygenase-2 (COX-2), inter-cellular adhesion molecule-1 (ICAM-1), vascular cellular adhesion molecule-1 (VCAM-1), T cell receptor-α (TCR-α), and Major Histocompatibility Complex (MHC) class II molecules (54, 55).

The activity of NF-κB is frequently deregulated in colon cancer and in inflammatory bowel diseases (IBDs), such as ulcerative colitis (UC) and Crohn's disease (CD). In human mucosal biopsy specimens, two main inflammatory pathways, NF-κB and mitogen activated protein kinase (MAPK) pathways, were activated by cytokine signaling (56). It was reported that butyrate is able to decrease pro-inflammatory cytokine expression by inhibition of IκB-α degradation in mucosal biopsy specimens from CD patients (57). Butyrate treatment of mouse gastric mucosa biopsies exposed to ethanol is also capable to negatively modulate the phosphorylation of NF-κB, p65, p38 MAPK and ERKs (58). It is documented that both TNF-α and interferon γ (IFN-γ) are involved in regulation of a series of metalloproteinases (MMPs) produced by inflamed mucosa. In 2016, Pedersen found that primary colon epithelial cells obtained by endoscopical biopsy from IBD patients express MMPs transcripts and secrete active proteolityc enzymes, suggesting that colonic epithelial cells, like myofibroblasts and immune cells, may contribute to local intestinal damage promoting tissue remodeling and leucocytes infiltration (58).

In a mouse model of UC, butyrate, acting as HDAC inhibitor and HAT activator inhibits the interferon-γ (IFN-γ)/ Signal transducer and activator of transcription 1 (STAT1) signaling pathways associated to the typical massive infiltration of CD3+ activated T lymphocytes in colonic mucosa. In colonocytes, STAT1 hyperactivation supports inducible Nitric oxide synthases (iNOS) mediated damage of colon mucosa with the restoration of a chronic inflammation typical of UC and the colorectal cancer progression. In this mouse model of UC, butyrate seems to function as a double-hit to suppress colonic inflammation: first, butyrate inhibits STAT1 hyperactivation in colonic epithelial cells to inhibit IFN-γ-mediated chronic damage; secondly, butyrate inhibits Fas promoter-bound HDAC activity to induce Fas promoter hyperacetylation and Fas upregulation, resulting in enhanced apoptosis of T cells, which leads to decreased accumulation of T cells in the inflamed colonic mucosa and consequent elimination of the source of inflammation (59). Butyrate also acts through a stimulation of peroxisome proliferator-activated receptor γ (PPARγ), a nuclear receptor highly expressed in colonic epithelial cells but also in colon cancer cell lines.

This effect was correlated both to HDAC inhibition and the AMPK activation. Upon activation, PPARs heterodimerize with 9-cis-retinoid X receptor (RXR) modulating the transcription of numerous target genes. PPARγ ligands as prostanoids including 15-deoxy-prostaglandin, polyunsaturated fatty acids, a variety of no steroidal anti-inflammatory drugs, and a new class of oral anti-diabetic agents, the thiazolidinediones markedly reduce colonic inflammation in a mouse model of inflammatory bowel disease (IBD) (60). Butyrate and PPARγ agonists reduce the paracellular permeability, promoting cell differentiation and tightening of the junction function in vitro (61). Finally an important butyrate target is represented by imflammasome. The inflammasome complex, consisting of a series of proteins, such nucleotide-binding oligomerization domain-like receptors (NLRPs), Acetyl-coenzyme A synthetase (ACS) and caspase-1 which promote inflammation in response to pathogenic microorganisms and sterile stressors, was found deregulated in chronic low-grade inflammation associated to obesity in humans. Recent data show that in mouse adipose tissue butyrate is capable to modulate the inflammasome through inhibition of in vivo activation of NLRP3 and caspase I. Inflammasome pathway mediated by NLRP3 was also found hyperactivated during gut inflammation and innate immune recognition of pathogens as well as intracellular and extracellular damage (62).

Clinical studies on butyrate anti inflammatory activity

Data from literature seem to suggest a wide spectrum of butyrate utilization as therapeutic molecule in a wide series of disorders. Oral administration of sodium butyrate is free from serious adverse events, although it results poorly palatable because of the unpleasant taste and odor. Therefore, most studies have focused on improving the palatability of the compound. The clinical utilization of butyrate is still limited by its rapid uptake and metabolism by intestinal mucosa and liver, resulting in a half life of 6 minutes and peak blood levels below 0.05 mM (63). For these reasons, butyrate is more indicated for the treatment of gastrointestinal pathologies. Recent data demonstrated that butyrate enemas prevent the atrophy of the diverted colon/rectum, improving the recovery of tissue integrity in patients undergoing colorectal cancer surgery (64). However, most clinical studies focused on UC patients. Hallert et al. instructed 22 patients with quiescent UC to add 60 g oat bran (corresponding to 20 g dietary fiber) to their daily diet. After four weeks of treatment they found a significant increase of fecal butyrate concentration with a significant improvement of abdominal symptoms (65). Vernia et al. performed a double blind, placebo-controlled multicenter trial in which 51 patients with active distal UC were treated with rectal enemas containing either 5-aminosalicylic acid (5-ASA) or 5-ASA plus sodium butyrate in a concentration of 80 mmol/L, twice a day.

The combined treatment with topical 5-ASA plus sodium butyrate significantly improved the disease activity score as compared to 5-ASA alone (66). These and other studies are concordant that the luminal administration of butyrate or the enhanced luminal butyrate production by the ingestion of dietary fiber ameliorates the inflammation and symptoms in UC patients. In UC, butyrate deficiency and down regulation of MCT1 in inflamed mucosa may cause the induction of the glucose transporter GLUT1 and a metabolic switch from butyrate to glucose oxidation that, together with altered oxidative status, could be associated to cancerogenesis susceptibility. However, evidences from pre-clinical studies show that oxidative stress, involved in both inflammation and in the process of initiation and progression of carcinogenesis in the colonic mucosa, can be modulated by butyrate (67, 68). During oxidative stress an imbalance between the generation of reactive oxygen species and the antioxidant defense mechanisms was reported, and this condition leads to a cascade of reactions in which cellular components (membranes, DNA, lipids and proteins) may get damaged. It has been demonstrated that locally administered butyrate in physiological concentrations increase the antioxidant Glutathione (GSH) and possibly decrease reactive oxygen species (ROS) production in colonic mucosa biopsies from healthy volunteers. A decreased expression of genes involved in uric acid metabolism was observed in biopsies after butyrate enema (69). Some studies indicated that daily local butyrate administration improves proctitis and prevents colon mucosa lesions in prostate cancer patients undergoing radiation therapy (70), even if another clinical trial shows no evidence of efficacy of butyrate enema in reducing the incidence, severity and duration of acute radiation proctitis (71). Butyrate was also tested in humans for the resolution of mucosa inflammation related to shigellosis, showing an anti inflammatory activity related to IL8 and IL1β down regulation and an up regulation of the antimicrobial peptide LL37 gene expression in inflamed mucosa (72). Finally, in a recent study on Apolipoprotein E (ApoE) knockout mice, oral butyrate was shown to be able to slow the progression of atherosclerosis by reducing adhesion and migration of macrophages and increasing plaque stability. These effects seem to be related to a reduction of CD36 marker in macrophages and endothelial cells, a decrease of pro-inflammatory cytokines and an inhibition of NFκB activation. For these reasons, authors proposed the utilization of this compound as an atheroprotective agent (73).

SCFA and exercise a dynamic duo for health: educational strategies for health promotion

The link between physical activity and gut microbioma remain to be completely understood, although in these years emerging evidences support the hypothesis that exercise induces a change in gut colonization. The first work in this field by Matsumoto et al. (2008) concluded that butyrate is increased in cecum of physical active rats (74). Evans et al (2008) found that exercise is able to alter gut microbioma togheter with diet composition. In particular, Evans observed distinct bacterial cluster for physically active mice fed with low fat or high fat diet (75).These results were partially confirmed in human through two studies: Barton et al (2017), analyzing 40 rugby players and 46 sedentary subjects, observed that professional athletes present differences in fecal metabolites and in healthy metabolic pathway associated with enhanced muscle turnover (eg. aminoacid biosynthesis and carbohydrate metabolism). In particular fecal concentrations of SFCA acetate, propionate and butyrate were higher than controls, supporting the insight into the diet-exercise paradigm (Barton et al. 2017, 76). Allen et al, in 2017 (77), analyzed the possibility that training can modulate the composition, functional capacity and metabolic output of gut microbioma in humans. Observing 32 lean and obese previously sedentary subjects that were recruited for a six week supervised endurance training, authors found that lean participants had a specific gut microbioma composition, with a prevalence of SCFA producing bacteria, but not obese partecipants. This effect in reversible if subjects interrupt the training. These evidences are in support of the so called “diet-exercise induced gut microbioma paradigm”. Educative strategies, related to a correct diet and exercise promotion for all life, seems to be relevant in order to maintain the healthy status and homeostasis. Among these, a long life promotion of a regular physical activity, consumption of high fiber and legumes diet and the weight control.

Conclusion

The human colon is continuously exposed to a variety of toxic stimuli deriving from diet, pharmacological treatments, pathogens, alteration of microbiota, etc. A grooving number of studies revealed that an enhanced butyrate production in the colon could result in an enhanced resistance against toxic stimuli, thus improving several processes like the barrier function, the antioxidant response, the maintenance of intestinal mucosa homeostasis, the modulation of visceral sensitivity and motility. Evidences show the relevance of butyrate administration for the treatment of gastrointestinal disorders, such as post-infectious irritable bowel syndrome (IBS), microscopic colitis, IBD, and diversion colitis. For its pro absorptive role, butyrate was adopted for the treatment of inherited intestinal diseases like congenital chloride diarrhea (78). For its HDAC inhibition activity, butyrate was proposed for the treatment of extra intestinal diseases like cystic fibrosis and beta-hemoglobinopathies. For what concerns this last point, some authors investigated the potential utilization of butyrate as a fetal globin gene-inducer in sickle cell anemia. A clinical trial was performed with an oral administration of a daily dose of 15 mg/kg of 2,2-Dimethylbutyrate sodium salt, but only a modest effect was registered with some adverse effects like headache, nausea and vomiting (79). Further clinical studies are required to establish pharmacodynamics, efficacy and safety of butyrate derivate compounds synthetized in order to improve palatability of this compound. Actually, potential fields of application of butyrate therapy still remain to be investigated, among these the urea cycle disorders, hypercholesterolemia, obesity, insulin resistance and ischemic stroke. Regarding physical activity at agonistic level, it's well know that intensive training without opportune recovery can induce overreaching and overtraining syndrome, with a clear symptomatology associated with a pro-inflammatory status. Actually, no study was proposed about the use of butyrate as supplement in order to facilitate recovery.

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