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Review

REVIEW OF THE EFFECTS OF SODIUM BUTYRATE ON OBESITY, INFLAMMATORY BOWEL DISEASE, PREGNANCY AND COLORECTAL CANCER

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ABSTRACT

Introduction and Purpose: Short-chain fatty acids (SCFAs), including butyric acid, acetic acid and propionic acid, are naturally produced in the large intestine by bacterial fermentation of insoluble carbohydrates and oligosaccharides. Butyric acid, which is the main source of energy for colon cells, has regenerative, cytoprotective and anti-inflammatory effects. Its physiological importance lies in maintaining the integrity and function of the intestinal epithelium, which protects the body against pathogens and oxidative stress. SCFA deficiencies resulting from low dietary fiber supply can lead to intestinal disorders. Supplementation with sodium butyrate, particularly using micro-encapsulation technology, enables efficient delivery of butyric acid to the gut, which may be beneficial in the treatment of inflammatory bowel disease and in the prevention of obesity and insulin resistance. Sodium butyrate (NaB) also has promising potential in the treatment of colorectal cancer (CRC), inducing apoptosis of cancer cells, increasing sensitivity to radiotherapy and chemotherapy and protecting healthy cells. SCFAs, especially butyrate, play a key role in reproductive medicine, oncology and gastroenterology, contributing to the maintenance of health and being potential therapeutic targets. The aim of this paper is to review the available literature on this topic.
Material and methods: The review was based on articles obtained from PubMed scientific database published from 2014-2024, using the following keywords: sodium butyrate, obesity, pregnancy, inflammatory bowel disease, colorectal cancer, SCFA.
Conclusions: Studies confirm the beneficial effects of sodium butyrate on metabolism, intestinal integrity and reduction of inflammation, opening up new possibilities in the treatment of metabolic disorders and intestinal diseases. However, further clinical studies conducted on humans are still needed, as most of the work to date has been conducted on mice and/or rats.

KEYWORDS: sodium butyrate; obesity; inflammatory bowel disease; colorectal cancer; pregnancy.

1. Introduction

Short-chain fatty acids (SCFAs), together with butyric acid, acetic acid and propionic acid, are produced naturally as a result of bacterial fermentation in the large intestine from insoluble carbohydrates and oligosaccharides and are supplied in small amounts with food [1,2]. From studies carried out as early as the '80s, it is known that butyric acid is the main and most important source of energy for colon cells, while also being a stimulant for their growth and differentiation [3]. However, of all the SCFAs found in the large intestine, it is the least abundant (1-10 mmol/l with the production of about 300-400 mmol SCFAs per day). The ratio of acetate to propionate and butyrate is 3:1:1 [4].

Butyric acid (CH_3-CH_2-CH_2-COOH) is an oily liquid soluble in water, with an unpleasant odor of rancid butter, while the sodium salt of butyric acid (sodium butyrate) has a solid state of matter, a milder odor and greater stability of the molecule. In aqueous solution, it readily dissociates to butyric acid, so it has found use as an ingredient in dietary supplements, milk replacers, animal feed additives, and is used in research on the mechanisms of action of short-chain fatty acids [5].

Butyric acid, physiologically, directly affects the intestinal flora and cells of the gastrointestinal wall, and indirectly, after absorption into the bloodstream, affects other tissues and organs. In preventing the body from invasion by pathogenic microorganisms, it is crucial to maintain the normal composition of the intestinal microbiota, as well as the integrity and function of the intestinal epithelium. As shown in studies, butyric acid has regenerative, cytoprotective, anti-inflammatory effects (including inhibiting the pro-inflammatory mediators TNF-α, IL-1ß, IL-6 and IL-8, and increasing the level of anti-inflammatory IL-10) and has a trophic effect on the normal intestinal mucosa as well as provides the main energy material for the cells that build it [6].

In various studies, its action has been shown to reduce the severity of diarrheal symptoms, restore normal gastrointestinal motility, also increase sodium and water absorption in the intestine, and significantly accelerate the regeneration of damaged intestinal epithelial cells thereby restoring the structural and functional integrity of the intestinal wall. This action protects the body from the movement of pathogenic microorganisms from the intestinal lumen into the bloodstream. For this reason, it is used as a support for primary treatment in inflammatory bowel disease or diarrhea [7,8]. It is also being studied for its effects on other diseases, including anticancer activity for colorectal cancer, relief of discomfort after radiation therapy, or effects on metabolic diseases. Ongoing studies also offer great hope for those struggling with obesity or insulin resistance [9,10].

2. How human diet influences the origin of butyrate

Butyrate production naturally occurs under the influence of fermentation of complex carbohydrates by bacteria colonizing the colon [11]. Butyrate-producing bacteria belong to the *Firmicutes* type and, according to some data, its most important producer is *Faecalibacterium prausnitzii* [12].

As is well known, the intestinal microflora plays a very important role in many diseases, and diet is one of its main modulators, influencing both the composition and function of the microbiota [13]. A diet rich in fiber and omega-3 fatty acids has a beneficial effect on the abundance of bacteria that produce short-chain fatty acids (SCFAs).

SCFAs include acetate, propionate and butyrate, which are formed by bacterial fermentation of resistant starch, simple sugars and polysaccharides [14]. There is a growing body of research indicating the regulatory role of SCFAs in lipid, cholesterol and glucose metabolism, and their influence, and action, on the integrity and immune response of the intestinal barrier [15]. The production of SCFAs occurs with intestinal anaerobic bacteria by saccharolytic fermentation of complex resistant carbohydrates (such as sugar alcohols, resistant starch, fructooligosaccharides, inulin and polysaccharides derived from plant cell walls) that are not digested and absorbed in the small intestine. These reactions result in the production of gasses, including hydrogen, carbon dioxide and methane [16]. Approximately 50-60 g of carbohydrates are required for the daily production in the gut of 500-600 mmol of SCFAs [17]. Also, some foods contain SCFAs, including: vinegar, sourdough bread and some dairy products such as butter, cheese, crème fraiche [18]. Different contents of SCFAs are reported depending on the part of the intestine, with concentrations ranging from 70 to 140 mM in the proximal part of the colon and decreasing to 20-70 mM in the distal part of the colon. Once absorbed, SCFAs are utilized in colonocytes or enter the bloodstream, from where they are transported to other organs [19].

Unfortunately, nowadays, with the increasing consumption of highly processed foods, poor in dietary fiber, the endogenous synthesis of SCFAs, including the important butyric acid, is significantly decreased. These deficiencies may lead to severe dysfunction of the intestinal mucosa, which may consequently impair the regenerative capacity of the intestinal epithelium and the maintenance of its integrity [20]. The relationship observed in studies confirms that a change in dietary habits leads to a decrease in the risk of colon cancer and colorectal disease, through an increase in natural butyric acid [20,21].

In situations where the diet cannot be enriched in dietary fiber because it exacerbates existing gastrointestinal complaints (in irritable bowel syndrome or ulcerative colitis, among others), sodium butyrate supplementation can be used [22]. As it is well known, butyric acid taken orally is very rapidly absorbed and metabolized in the initial gastrointestinal tract, so attention should be paid to the form of the dietary supplement to ensure that it can reach the downstream sections of the intestine. An effective method has been developed using microencapsulation technology, which involves encapsulating the sodium butyrate molecules in lipid microbeads and these in a gel capsule. This technology provides an effective and safe way to deliver sodium butyrate to the downstream parts of the intestine. Due to the physiological activity of the gastrointestinal tract, these preparations are best taken after a meal, when the secretory activity of the pancreas, whose lipases

gradually release butyric acid from the microbeads, increases [23].

Preparations containing sodium butyrate together with specially selected probiotic *Lactobacillus* strains (*L. rhamnosus* and *L. acidophilus*) and *Bifidobacterium* strains (*B. longum*, *B. bifidum*, *B. lactis*) are also available on the market. They are particularly helpful in relieving the discomfort associated with irritable bowel syndrome and after antibiotic therapy to accelerate the restoration of the normal intestinal bacterial flora [24,25,26].

3. Obesity and research into the effects of sodium butyrate supplementation

Obesity is a disease affecting more and more people worldwide, reaching pandemic status. As a result, the predisposition to other comorbidities, including cardiovascular disorders, dyslipidemia, type 2 diabetes or non-alcoholic fatty liver disease (NAFLD), increases significantly. From the increasing amount of research conducted on obesity, its multifactorial causes are emerging. Both environmental factors and individual predisposition influence the occurrence of different types of obesity. Some studies also point to the decisive role of the gut microflora and the changes it undergoes, providing a causal link between environmental factors and the onset of obesity. As mentioned earlier, the intestinal microflora influences the production of short-chain fatty acids (SCFAs) in the intestinal lumen, which contribute to, among other things, the maintenance of normal intestinal homeostasis and the regulation of the immune response [27]. Unfavorable changes in the intestinal microbiome result in the entry of lipopolysaccharides (LPS) through the leaky intestinal barrier. This process contributes to the induction of inflammation in tissues. A study was conducted to investigate the effects of external supplementation of sodium butyrate (NaB) on the immuno-metabolic profile of adipose tissue and its effects on the metabolic and inflammatory status of adipose tissue. The study was conducted on two groups of mice, with the group consuming a high-fat diet (HFD) enriched with sodium butyrate showing a better metabolic profile compared to the group fed only HFD. The study also showed that NaB administration improved glucose tolerance and insulin sensitivity. As is well known, leaky gut and the entry of LPS into the circulation affect the presence of inflammation in tissues. In the FITC dextran permeability assay, increased intestinal barrier integrity was confirmed after NaB treatment, which increases the expression of proteins responsible for tight junctions in the intestinal lining. The potential role of NaB in alleviating inflammation was also investigated. After evaluating immune cells from the vascularised fraction of adipose tissue by flow cytometry, significantly increased numbers of M2 macrophages (CD206+) and Treg (CD25+) were revealed compared to the M1 macrophage population and CD4+ T cells, respectively, in NaB-treated mice. These studies demonstrate a potential beneficial role for sodium butyrate in ameliorating metabolic abnormalities and pro-inflammatory cytokine secretion associated with obesity. Sodium butyrate inhibits the high glucose-induced production of inflammatory cytokines by regulating histone acetyltransferase and histone deacetylase in monocytes [28,29]. A high-fat diet with sodium butyrate has been shown to reduce the ratio of fat to fat-free mass, slightly improve dyslipidaemia and restore oral glucose tolerance. In pre-diabetic HFD-fed mice, NaB increased basal energy expenditure, but showed no effect in control mice. At the same time, no significant changes were observed in hypothalamic orexigenic and anorexigenic gene expression or motor activity [30]. In a subsequent study in mice fed HFD, sodium butyrate abolished its deleterious effects, alleviating insulin resistance, intestinal dysfunction, inflammation and obesity-induced hepatic steatosis. The study also showed a possible mechanistic effect of NaB on promoting fat thermogenesis via a mechanism of increasing local sympathetic innervation of adipose tissue and blocking the β3-adrenergic signaling pathway by 6-hydroxydopamine abolishing NaB-induced thermogenesis [31]. Furthermore, butyrate had a significant effect on white adipose tissue (WAT) reducing its weight and lipid saturation compared to HFD-fed mice without NaB supplementation [32]. The effects of butyrate on microglial activation and hypothalamic inflammation induced by excessive food intake were also investigated, affecting feeding disorders, energy homeostasis and obesity pathogenesis. As shown in the study, oral NaB supplementation significantly reduced inflammatory cytokine expression, decreased HFD-induced microglia, endoplasmic reticulum stress, neuronal apoptosis and neuropeptide Y (NPY) expression in the hypothalamus of mice. NaB also exerted anti-oxidant effects, preventing the production of reactive oxygen species (ROS) in microglia [33]. Studies in obese people (BMI ≥ 30 kg/m^2) qualified for laparoscopic sleeve gastrectomy have confirmed that weight loss and ex vivo SCFAs treatment are effective in controlling systemic inflammation in obesity. Significant reductions in TNF-α and IL-6 were observed, as well as altered FFAR and HDAC mRNA expression in monocytes and macrophages from blood and visceral adipose tissue of obese subjects [34]. In 2021, a triple-blind, randomized, controlled trial (RCT) involving obese people aged 18 to 60 years was launched in Iran to evaluate the effects of sodium butyrate supplementation on PGC-1α, PPARα and UCP1 gene expression levels, metabolic parameters and anthropometric indices. It is worth following this study further, as its results may help fill the gap in research on the effects of butyrate on obesity in humans [35]. Another paper on selected health markers caused by overweight and obesity in children showed that they had different fecal enzyme activities and fatty acid profiles compared to normal-weight children. The study checked fecal enzyme activity, SCFAs concentration and branched chain fatty acid (BCFA) concentration. Increased BCFA concentrations and higher activity of potentially harmful enzymes (such as β-glucosidase and β-glucuronidase) were observed in the group of obese children, compared to the group of normal-weight children. At the same time, normal-weight children had higher values of α-glucosidase and α-galactosidase activity, as well as higher concentrations of lactic acid and SCFAs (particularly butyric acid and formic acid), compared to the group of obese children [36]. The effect of oral butyrate supplementation, as an adjunct to standard treatment of childhood obesity, was also investigated. Its main outcome was a decrease in BMI greater than or equal to 0.25 SD after 6 months of NaB treatment. There were also better results in the butyrate group on secondary outcomes, which were waist circumference, levels of

fasting glucose, insulin, ghrelin, IL-6, total cholesterol, homeostatic model for assessing insulin resistance (HOMA-IR) and relative microRNA 221 expression [37].

4. SCFAs and pregnancy

Many metabolic changes occur during pregnancy, including changes in the phylogenetic diversity of the intestinal microflora. SCFAs, which are metabolic products of intestinal bacteria, affect normal homeostasis, immune function, and lipid and carbohydrate metabolism in the pregnant woman's body [38]. Abnormalities in the gut microbiota can result in elevated glucose levels and potentially gestational diabetes mellitus (GDM), as a factor associated with metabolic changes. Several factors contribute to the insulin resistance (IR) seen in pregnancy, including physical inactivity, obesity, placental hormone effects, and genetic and epigenetic changes. Physiologically, IR facilitates the availability of maternal energy resources to the developing fetus, while pathological IR contributes to the incidence of neonatal obesity [39]. One of the factors explaining the development of pathological IR and the development of GDM is an abnormal diet that changes the qualitative and quantitative composition of the intestinal microbiota responsible for the production and proportion of SCFAs. As a result, lipid and glucose transport across the placenta increases, leading to beta-oxidation and inflammatory stress in the developing fetus. The result is excessive lipogenesis and fat accumulation, which cause symptoms of metabolic syndrome in the newborn [40]. Also, other abnormalities are observed, including elevated cytokine levels and changes in the early cytokine response of innate immune cells early in life [41,42]. A significant accumulation of macrophages in the placenta is also observed in obese pregnant women. They cause the production of pro-inflammatory cytokines and adipokines, such as IL-6, leptin, TNF-α, monocyte chemotactic protein 1 and TLR4. The presence of the inflammatory process contributes to an increase in the release of free fatty acids into the fetal circulation, disrupting fetal growth and development. Abnormalities in the intestinal microflora can serve as an early biomarker of GDM, particularly characteristic and evident in the second trimester of pregnancy. In mice subjected to implantation of the gut microflora of pregnant women in the third trimester of pregnancy, IR and weight gain were observed. These results reflected the metabolic changes occurring in pregnant women. Supplementation with probiotics containing *Bifidobacterium* and *Lactobacillus* may improve health outcomes, including maintaining normal SCFAs concentration ratios, especially when lifestyle modification, diet and exercise are not effective.

Changes in the microbiome, such as a reduction in the number of SCFAs-producing bacteria, both quantitative and qualitative (less diversity of resident bacteria), have been observed in people with hypertension. SCFAs, through a direct effect on vasodilation, and an indirect effect through plasminogen activator inhibitor-1 (PAI-1), may influence the maintenance of normal blood pressure. Similar relationships have been reported in pregnant women, where altered gut microflora composition and butyric acid production correlated with increased systolic as well as diastolic blood pressure [43]. Chang et al. concluded that butyrate has a blood pressure-lowering effect in pregnant women with hypertension, both at the beginning and later stages of pregnancy [44]. These studies also suggest a putative role for butyrate in the treatment of preeclampsia (PE). Women with pregnancies complicated by hypertension, including PE and HELLP syndrome, have been observed to have elevated blood levels of PAI-1 and its increased expression in the placenta [45,46]. SCFAs, through induction of the endothelium-dependent peroxisome proliferator-activated lipid metabolism (PPARγ) pathway, are suspected to play a key role in preventing endothelial dysfunction. Despite the transplacental effects of maternal bacteria and their metabolites on the developing fetus, their role is still not fully understood and requires further research [47].

5. Inflammatory bowel disease and the regulatory role of sodium butyrate

Inflammatory bowel disease (IBD) is an idiopathic autoimmune inflammatory bowel disease, and affects the ileum, colon and rectum. The two main clinical forms of IBD include Crohn's disease (CD) and ulcerative colitis (UC) [48]. In both disease entities, there is repeated epithelial damage and the presence of an inflammatory cell infiltrate in the lamina propria, accompanied by immune dysregulation, leading to repeated cycles of remission and recurrence of inflammation [49]. As has been shown in many studies, IBD is closely associated with disturbances in the balance of the gut microbiome. IBD patients have a reduced presence of bacteria (among others, *F. prausnitzii* and *Roseburia intestinalis*) responsible for SCFAs production in the intestinal mucosa and feces, compared to healthy individuals [50-53]. To date, treatment of patients with IBD is based on attenuating the body's inflammatory response. Unfortunately, a small number of patients succeed in achieving and maintaining clinical and endoscopic remission [54]. New therapeutic approaches that take into account the key role of the intestinal microflora in IBD are being investigated, involving the use of prebiotics, probiotics, antibiotics or fecal microbiota transplantation. The results are inconsistent and require further research, hence SCFAs and the bacteria that produce them offer great hope [55].

SCFAs (as inhibitors of histone deacetylation) at the cellular level can directly or indirectly affect cellular processes such as cell proliferation, differentiation and gene expression, and have immunomodulatory effects on innate and acquired immune cells [49, 56]. Receptors for SCFAs are present throughout the human body, highlighting their important role for the body. There are G protein-coupled receptors (GPCRs) such as GPR41 (known as free fatty acid receptor 3, FFAR3) and GPR43 (or FFAR2) and GPR109A (also known as hydroxycarboxylic acid receptor 2, HCAR2) - which are expressed in various organs, including the intestine, kidney, heart and on immune cells. This indicates that butyrate is involved in the regulation of metabolism and inflammation through activation of the anti-inflammatory signaling cascade [57]. GPR109A is a butyrate-activated receptor that is expressed in colonic epithelial cells. It promotes the anti-inflammatory properties of colonic macrophages and dendritic cells in C57BL/6 mice, induces differentiation of T cells producing Treg and IL-10, and has an inhibitory effect on colonic inflammation and carcinogenesis [58]. Another pathway through which SCFAs affect cellular

glucose metabolism, lipid metabolism and immune function are transporters such as the monocarboxylate transporter (MCT1) and sodium-conjugated MCT (SMCT1) [51,59].

One more study conducted on the effects of butyrate on ulcerative colitis found that it increased mucin production and the percentage of mucus-secreting cup cells in the colonic crypt in a macrophage-dependent manner. SCFAs influence intestinal cells by showing high expression of GPR43, functioning as regulators of the physical barrier, antimicrobial peptides, cytokines and chemokines. This suggests that butyrate has a positive effect on regulating epithelial barrier integrity and may serve as a potential therapeutic target for the treatment of UC [60,61]. The fecal microflora of European children susceptible to IBD was less diverse and deficient in SCFAs-producing bacteria compared to African children [62]. Also, evaluation of the Western diet has shown that it leads to a decrease in GPR43 expression in CD patients and in mice fed a high-fat diet rich in simple sugars. Also, microbiome disruption, reduction of SCFAs and increased risk of colitis were observed [63]. Through immune regulation and maintenance of the epithelial barrier, GPCRs protect against intestinal inflammation. More severe dextran sodium sulfate (DSS)-induced colitis was observed in GPR43-/- and GPR109A -/- mice than in controls [58, 64]. A number of older studies have signaled the beneficial effects of SCFAs in patients with IBD, such as SCFAs infusions of a mixture of sodium acetate, sodium propionate and sodium butyrate, which increased the efficacy of classical IBD treatments [65].

6. Association of sodium butyrate with colorectal cancer

As one of the most common cancers in the world, colorectal cancer (CRC) has a high mortality rate, hence tools to predict its risk are very important for early diagnosis. CRC is characterized by an accumulation of genetic and epigenetic changes, leading to uncontrolled division and dysplasia in colorectal cells [66]. Among the risk factors for colorectal cancer is an impaired composition of the intestinal microflora [67-69]. Studies of CRC patients have shown that these individuals have a reduced percentage of butyric acid-producing bacteria and probiotic bacteria. In contrast, they have a higher percentage of bacteria responsible for gastrointestinal inflammatory diseases and bacteria that produce toxins and carcinogenic metabolites. Despite prospective and case-control studies, no single microorganism responsible for the development of CRC can be identified [70]. The use of sodium butyrate (NaB) may be a promising adjunct to well-known therapies such as surgery and neoadjuvant therapy [71]. Recent studies show that butyrate can induce apoptosis of colorectal cancer cells [72]. In a study by Xiao et al. they tested the effect of exposing colon cancer cells (HCT116) to NaB at a dose of 10 mmol/L for 24 hours. The colon cancer cells had also previously been treated with an ERK or siRNA inhibitor. The study showed that butyrate ultimately induced apoptosis of colon cancer cells [73]. Another study, conducted by Elimrani et al. on colon cancer cells (SW480), confirmed the anticancer effects of butyrate [74]. Also, Roy et al. demonstrated an inhibitory effect on Caco-2 cell proliferation and apoptosis of colon cancer cells using butyrate at a dose of 2.5-20 mM (as well as carnitine) [75]. The effect of butyrate on other CRC treatments, including radio- and chemotherapy, has also been studied. Butyrate has been shown to increase the sensitivity of cancer cells to radiation while protecting healthy cells [76]. Additionally, butyrate can enhance the effects of chemotherapy by potentiating the effects of irinotecan [77]. Similar effects, i.e. enhancing the effects of chemotherapy, were obtained in another study on the effects of butyrate together with 5-fluorouracil on CRC cells [78].

A very common side effect of chemotherapy is mucositis. In a study conducted in a mouse model, the use of butyrate was found to be positively correlated with a reduction in the side effects of 5-fluorouracil treatment [79]. The effect of NaB on the intestinal microflora in mice with colorectal cancer metastasis to the liver was also investigated. The composition of the intestinal microflora was assessed by sequencing the 16SrRNA gene. The study showed a beneficial effect of butyrate on modulating the intestinal microflora, and the immune system by decreasing the number of Treg lymphocytes and increasing the number of NK cells, as well as helper T cells [80]. Ongoing studies suggest that NaB is worth considering as a promising new option as a potential adjunct in the complex, multidisciplinary treatment of colorectal cancer. NaB supplementation, in combination with ingredients that stimulate butyrate production, such as dietary fiber, as well as omega-3 fatty acids, may alter the intestinal microflora and even the tumor microenvironment [81].

7. Conclusions

In light of the information discussed, several important conclusions can be made. First, short-chain fatty acids (SCFAs), especially butyrate, are of key importance in various medical fields, including reproductive medicine, oncology and gastroenterology. Studies show that SCFAs have beneficial effects on metabolism, inflammation and intestinal integrity, opening up new therapeutic possibilities for the treatment of metabolic and intestinal diseases.

In addition, there is a strong correlation between gut microbiota and body health, especially in the context of pregnancy and intestinal diseases. Microbiota disorders can lead to serious consequences, such as insulin resistance in pregnancy, gestational diabetes, hypertension and inflammatory bowel diseases. The use of probiotic supplementation, especially those containing strains of SCFAs-producing bacteria, can provide health benefits by regulating the production of these acids.

Finally, sodium butyrate, which is one of the SCFAs, has shown promise in the treatment of colorectal cancer. Its ability to induce apoptosis of cancer cells and increase their sensitivity to radiotherapy and chemotherapy is an important tool in the fight against this disease.

The conclusion of the above review is the need for further research on the role of SCFAs in health and disease to better understand their mechanisms of action and to use them in clinical practice as an effective therapeutic tool.

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