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Butyric acid: what is the future for this old substance?

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Summary

In this brief review, we present some data from the literature on butyric acid and some of its more interesting potential uses, especially in the field of gastroenterology. Due to its principal characteristics, butyric acid is primarily used for pathologies of the colon (functional, inflammatory). Although only preliminary data are available, butyric acid may also have interesting extraintestinal applications, such as in the treatment of haematological, metabolic, and neurological pathologies.

Key words: *butyric acid; inflammatory bowel diseases; ulcerative colitis; Crohn's disease; irritable bowel syndrome; beta-thalassemia; urea cycle disorders; obesity*

Introduction

Butyric acid (BA) is a carboxylic acid with the formula CH_3-CH_2-CH_2-COOH. It is frequently used in the veterinary field, especially in ruminant animals. Together with other short-chain fatty acids (propionic acid and acetic acid), BA is the principal source of energy produced by ruminal fermentation of cellulose and starch. In the field of zootechnics, butyric acid is used to improve the growth of bovine animals [1]. In humans, BA is synthesised by the colonic microflora (microbiota) during fermentation of digestible fiber, such as cereal flour, inulin, and psyllium [2]. In humans, the effects of BA can be subdivided into intestinal and extraintestinal. Intestinal effects include: regulating transepithelial transport, improving the inflammatory and oxidative states of the intestinal mucosa, reinforcing the mucosal barrier, modulating visceral sensitivity and motility, and preventing and inhibiting colon carcinoma. Extraintestinal effects are less well known; they have been studied *in vitro* and in animal models and sometimes even in humans. Currently investigated effects include: haemoglobinopathies, hypercholesterolaemia, reducing resistance to insulin (in animal studies), and reducing ischemic stroke (in animal studies).

Intestinal effects

The intestinal ecosystem is comprised of epithelium, immune system cells, enteric neurons, microbiota, and prebiotics. Our knowledge of the intestinal microbiota remains quite limited due to the difficulty of identifying the numerous bacterial strains present [3]. The human intestine hosts a large quantity of bacteria (approximately 10^{13}–10^{14}) and could thus be termed a "superorgan" as the human body is comprised of approximately 10^{14} cells [4, 5].

BA is one of the short-chain fatty acids produced by the colon, in particular, by the proximal colonic microbiota and constitutes one of the primary sources of energy for colonocytes [2]. It enhances the absorptive and antisecretive capabilities of the intestinal mucosa. Clausen et al. [6] demonstrated that some cases of antibiotic-associated diarrhea are related to inhibited bacterial fermentation to short-chain fatty acids, leading to reduced absorption of water and sodium. BA has also been shown to stimulate the production of mucin – a specific defense of intestinal mucosa – through increased expression of mucin genes, such as MUC2 [2].

BA has a double effect on cell growth, defined as the "butyrate paradox"; it stimulates physiological proliferation of normal enterocytes, whereas it inhibits cell proliferation in a colon carcinoma cell line *in vitro* by enhancing histone acetylation [3]. The possible preventive effects of BA acid are attractive, especially considering the adverse effects of drugs used to prevent colorectal cancer, such as aspirin and cyclooxygenase type 2 (COX 2) inhibitors. The administration of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), such as celecoxib, has resulted in significant gastrointestinal and cardiovascular toxicity. Furthermore, COX2 inhibitors are very expensive. These issues with other colorectal cancer preventative measures make it very appealing to think that BA could be used in high-risk patients (those with familial adenomatous polyps or hereditary non-polyposis colorectal cancer) and those over age 60 (who are at higher risk due to age) [7].

BA has anti-inflammatory effects through inhibition of NF-κB, which reduces the expressions of cytokine genes, including TNFα, IL1β, IL2, IL6, IL8, and IL12. Clinical experiences indicate that antioxidant activity of BA reduces

reactive oxygen species and increases the amount of reduced glutathione [8]. BA's anti-inflammatory action has been the subject of some interesting studies regarding its use in inflammatory bowel diseases (IBD) as well as in radiation proctitis. Almost all available data is derived from small studies on ulcerative colitis, where it has been administered primarily by enema (table 1) [9–16]. Sodium butyrate is usually the form administered in conjunction with mesalazine for mild to moderate IBD; however, Assisi et al. utilised a slow-release preparation of calcium butyrate and inulin (NMX formulation) [9]. The majority of reported studies performed post-treatment evaluation using clinical, endoscopic, and histologic data, but Assisi et al. [9] and Steinhart et al. [15] used only a clinical score (ulcerative colitis disease activity index; UDCAI).

The studies in table 1 have several limitations, including the fact that not all are randomised, the small numbers of patients studied, the different methods of administering BA (oral/enema), and the different criteria for endpoint evaluation. It should also be noted that in the randomised studies reported in table 1, the number of patients treated with BA is only 50% of the total number of patients treated, except for in the cross-over study by Scheppach et al. [16].

One interesting application of BA involves its use in irritable bowel syndrome (IBS), of which knowledge is still fragmentary, especially regarding the enteric nervous system and its regulation. IBS has a prevalence of about 11.5% in the European population and therefore has significant impact on healthcare [17]. Preliminary *in vitro* and animal studies demonstrate activity of BA on colonic motility through choline acetyltransferase [1], but there is limited data in humans. Vanhoutvin et al. [18] administered sodium butyrate as enema versus placebo to assess pain, sensation of urgent defecation, and discomfort as measured by a barostat in 11 healthy volunteers (3 males and 8 females). The authors conclude that butyrate administered as enema (especially in doses of 100 mmol/L) increases the pressure threshold before causing pain or discomfort – although the study did not report the effect of patient age, and the results only refer to healthy subjects. In contrast, studies in animals (rats) show visceral hypersensitivity to butyrate enemas; thus, there is a need for randomised, controlled studies measuring the impact of BA on IBS [19].

One pharmaceutical technical problem regarding the use of butyrate is that most commercially available formulations do not have standardised release. The study by Assisi et al. [9] used an oral formulation that releases BA in the form of calcium butyrate in the colon, which permitted a more practical (oral) and standardised administration.

This brief overview illustrates the favourable effects of BA that have been observed in the clinic. The etiopathogenetic mechanisms are not yet well understood. Although there are a few reports in the literature of the use of BA in IBD, new clinical studies are needed to confirm these data and to clarify its use for other conditions, such as IBS and cancer prevention. The possibility of using BA to prevent colorectal cancer is obviously of great clinical interest and merits systematic investigation.

Extraintestinal effects

BA increases the production of fetal haemoglobin (HbF) in β-thalassemia patients and in those with sickle cell anaemia, reducing ineffective erythropoiesis. Generally speaking, an increase in HbF reduces the α/non-α chain imbalance, thus improving the anaemia. BA is a histone deacetylase inhibitor that, in vitro, stimulates synthesis of the γ haemoglobin chains and sometimes of α chains; this occurs in a different manner, according to the type of disease (β-thalassemia or sickle cell anaemia) [20]. In 2011, Perrine et al. published a phase I, randomised, double-blind study that tested the safety and blood effects (reticulocytes and HbF assays) of a BA derivative (sodium 2,2-dimethylbutyrate) given orally in healthy volunteers. The results are quite encouraging in terms of safety and statistically significant increases in reticulocytes, indicating favourable prospects for use in patients with β-thalassemia and sickle cell disease [21, 22].

BA can also function as an ammonia scavenger in patients with enzymatic deficit of the urea cycle. These patients have an ornithine transcarbamylase (mitochondrial enzyme) deficiency, which develops at different ages, in both newborns and adults, and involves predominantly neurological symptoms that range from headache to coma [23, 24]. Ornithine transcarbamylase is expressed in the liver and intestine, and is encoded by a gene located on chromosome Xp21.1. The initial diagnosis of deficiency is based on hyperammonaemia, and can later be confirmed by testing of amino acids, such as citrulline (lower) and glutamine and alanine (higher). BA acts on the conjugation of glutamine and successive excretion in urine. Burlina et al. administered sodium phenylbutyrate (median dose of 352 mg/kg/day in three to four divided doses) to 9 patients with ornithine transcarbamylase deficit, and followed them for 26 months. During the study, no episodes of hyperammon-

Table 1

Author	Year	N. Pts.	Randomised	U.C./ Crohn	Enema/ oral	Mesalazine/ Sulfasalazine	Duration	Butyrate dose	Outcome
Assisi RF(9)	2008	216	No	U.C.	Oral	Yes	6 months	921 mg/day	82.4% (improved)
Di Sabotino A(10)	2005	13	No	Crohn	Oral	Yes	8 weeks	4 gr/day	69% (improved)
Vernia P(11)	2003	51	Yes	U.C.	Enema	Yes	6 weeks	160 mmol/day	S.
Vernia P(12)	2000	30	Yes	U.C.	Oral	Yes	6 weeks	4 gr/day	N.S.
Steinhart AH(13)	1996	38	Yes	U.C.	Enema	Yes (28/38)	6 weeks	80 mmol/day	N.S.
Vernia P(14)	1995	40	Yes	U.C.	Enema	Yes	6 weeks	200 ml/day (mixture)	S.
Steinhart AH(15)	1994	10	No	U.C.	Enema	Yes	6 weeks	80 mmol/day	60% (improved)
Scheppach W(16)	1992	10	Yes	U.C.	Enema	Yes (3/10)	2 weeks	100 mmol/day	S.

N.S. = not aignificant; S. = significant

aemia requiring hospitalisation occurred, it was possible to increase the patients' intake of protein, and no side effects were attributable to the therapy [25].

At another metabolic level, BA can down-regulate the expression of genes involved in the biosynthesis of cholesterol and triglycerides and modulate apolipoprotein biogenesis and lipoprotein assembly [26]. Metabolic activity of short-chain fatty acids (including BA) is mediated by individual intestinal microbiota. In both animals and humans, increasing evidence is emerging to support the relationship between obesity and type of intestinal microbiota [4, 27]. Sometimes the published articles present conflicting results. Obese individuals have a lower quantity of intestinal *Bacteroides* species and more *Firmicutes* but some authors observed more *Bacteroides* in overweight and obese subjects [28]. BA binds receptors, including protein-coupled receptors (e.g., Gpr41), that are present on intestinal endocrine cell surfaces, and stimulate these cells to produce peptide YY, which in turn inhibits gut motility and increases satiety [29, 30].

Gpr41 is expressed also in adipose tissue and short-chain fatty acids stimulate leptin production both in cultured adipocytes and in the whole animal [31]. Animal studies demonstrate that BA and propionate can reduce obesity and insulin resistance in Gpr41-deficient mice with independent mechanism [32]. Furthermore, studies in animals (rats) showed that sodium butyrate can stimulate neuronal proliferation in zones that have undergone cerebral ischemia [33].

Conclusions

In conclusion, BA is a substance with interesting possibilities for gastroenterological therapies (e.g., IBD, IBS, and colorectal cancer) as well as for haematological diseases (e.g., β-thalassemia), metabolic diseases (e.g., enzymatic deficit urea cycle and obesity), and vascular stroke. Since BA cannot be patented, it is of little interest to the pharmaceutical industry except in regards to developing different types of release formulations, as has been done in the veterinary field.

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