Review paper

# Butyric acid in functional constipation

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## Abstract

Butyric acid, a short-chain fatty acid, is a major energy source for colonocytes. It occurs in small quantities in some foods, and in the human body, it is produced in the large intestine by intestinalkacteria. This production can be reduced in some cases, for which butyric acid supplementation may be useful. So far, the use of butyric acid in the treatment of gastrointestinal disorders has been limited because of its specific characteristics such as its rancid smell and rapid absorption in the upper gastrointestinal tract. In the Polish market, sodium butyrate has been recently made available, produced by the modern technology of microencapsulation, which allows the active substance to reach the small and large intestines, where butyrate easily dissociates into butyric acid. This article presents the potential beneficial mechanisms of action of butyric acid in defecation disorders, which are primarily associated with reductions in pain during defecation and inflammation in the gut, among others.

## Butyric acid

Butyric acid (butanoic acid [$C_4$]) is a short-chain fatty acid (SCFA). It is considered the main energy substrate for colonocytes and a factor that stimulates their growth and differentiation [1]. This oily liquid is easily water soluble and has an unpleasant, rancid smell. The sodium salt of butyric acid (sodium butyrate) is a solid that has a more stable molecule and less unpleasant odour than acid. Moreover, it easily dissociates to butyric acid in an aqueous solution. Therefore, it has been widely used in scientific studies on mechanisms of SCFA activities. Butyric acid naturally occurs in butter, hard cheeses (e.g., parmesan), milk (especially goat's and sheep's), yoghurts, cream, and in some other fermented foods (e.g. sauerkraut, pickled cucumbers, and fermented soy products) but in very small and insignificant amounts for gut health. In the human body, butyrate is produced in the large intestine together with other SCFAs. Approximately 83% of the total SCFAs in the large bowel of mammals are acetic, propionic, and butyric acids [2]. The total concentration of these acids in the intestinal lumen ranges from 60 mmol/kg to 150 mmol/kg. The amounts of faecal SCFA are relatively constant in the following order of decreasing concentration: acetate > propionate ≥ butyrate [3].

## Production and absorption of short-chain fatty acids, particularly butyric acid

Short-chain fatty acids are produced by bacterial fermentation of non-digestible carbohydrates such as non-starch polysaccharides, resistant starch, oligosaccharides (prebiotics (inulin) and oligofructose), disaccharides (lactose, stachyose, and raffinose), and sugar alcohols (sorbitol and mannitol) [4]. Butyric acid is mainly formed from the decomposition of pentoses contained in whole-grain products (wheat bran, whole-wheat bread, pasta, and brown rice), legumes, vegetables, and fruits [5]. In particular, resistant starch is regarded as butyrogenic [2], and examples of products rich in this dietary fibre are partially milled grains and seeds, uncooked and cooked-and-chilled potatoes, green bananas, vegetables, and legumes (e.g. lentils). The following are butyrate-producing bacterial species: *Clostridium* spp., *Eubacterium* spp., *Fusobacterium* spp., *Butyrivibrio* spp., *Megasphaera elsdenii, Mitsuokella multiacida, Roseburia intestinalis, Faecalibacterium prausnitzii*, and *Eubacterium hallii* [6]. The daily production of SCFA in the large intestine in healthy humans ranges from 300 mmol to 400 mmol, and physiological concentrations of butyric acid in the intestinal contents range from 1 mmol/l to 10 mmol/l [7, 8].

Short-chain fatty acids are rapidly absorbed in the colon, and butyric acid is absorbed mainly in the ascending colon. Absorption occurs due to the high concentration gradient between the colonic lumen and the colonocyte, which occurs by either active or passive transport [9]. Butyric acid is completely metabolized in the colonic epithelial cells; therefore, only a small amount can enter the bloodstream [7].

## Functional constipation

Constipation is a frequent, chronic gastroenterological problem that has many varied symptoms and thus has several clinical definitions. Functional constipation becomes a concern when it develops into a chronic disorder characterized by abnormal defecation, that is, persistent difficult or seemingly incomplete defecation and/or infrequent bowel movements, without any anatomical or physiological causes. It may have a neurological, psychological, or psychosomatic cause.

The constipation problem is widespread; however, accumulating reliable epidemiologic data is difficult because of the varied medical definitions and symptoms reported worldwide. The most common symptoms reported by the patients are bloating, abdominal pain, malaise, various stool consistencies, prolonged/excessive straining, and unsatisfactory defecation. According to a systematic review of the literature conducted in 2008, constipation affects, on average, 17.1% of the general population of Europe. This value depends on the studied population, ranging from 0.7% to 81%. The problem was observed to be more common in women [10]. Table I shows the diagnostic criteria, so-called Rome III criteria, for functional constipation in adults [11].

**Table I.** Rome III criteria for functional constipation

| Diagnostic criteria for functional constipation in adults |
|---|
| 1. Must include two or more of the following: |
| a) Straining during at least 25% of defecations |
| b) Lumpy or hard stools in at least 25% of defecations |
| c) Sensation of incomplete evacuation for at least 25% of defecations |
| d) Sensation of anorectal obstruction/blockage for at least 25% of defecations |
| e) Manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor) |
| f) Fewer than three defecations per week |
| 2. Loose stools are rarely present without the use of laxatives |
| 3. Insufficient criteria for irritable bowel syndrome |
| *Criteria must be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis* |

Many different possible causes of functional constipation exist, from incorrect nutritional habits to low physical activity and primary motor dysfunctions due to colonic myopathy or neuropathy. Constipation can also be related to evacuation disorder, which is a secondary problem.

Management of chronic constipation is first based on recommending lifestyle changes including a high-fibre diet (also fibre supplements), increasing fluid intake, and increasing physical activity. Moreover, keeping a stool diary and bowel training may help. Furthermore, it is well documented that adding osmotic laxatives such as polyethylene glycol or lactulose can increase stool frequency and improve symptoms of constipation [12]. Sometimes prokinetic drugs are recommended; however, their effect is limited to the upper gastrointestinal tract [13].

## Possibilities of butyric acid application in functional constipation

So far, despite the promising results of several studies on the mechanisms of action of butyric acid, particularly its role in the metabolism of intestinal epithelial cells, functional aspects of the intestine, and anti-inflammatory and regenerative properties, studies that evaluate its efficacy strictly in functional constipation have not been conducted.

Some studies have shown potential therapeutic effects of butyrate on constipation, such as reducing pain during defecation. Banasiewicz *et al.* [14] performed a randomized controlled study in a group of 66 patients with irritable bowel syndrome (IBS) with constipation. They observed a statistically significant reduction in pain during defecation in patients who received microencapsulated sodium butyrate at a dose of 2 × 150 mg per day for 12 weeks compared with those who received placebo. After 4 weeks, a significant decrease in pain during defecation was reported by the study group (0.18 ±0.4 vs. 0.59 ±0.5, $p = 0.0032$), which was maintained for 12 weeks (0.15 ±0.36 vs. 0.59 ±0.50, $p = 0.0002$). In the 12$^{th}$ week, statistically significant changes in stool consistency (0.18 ±0.39 vs. 0.4 ±0.5, $p = 0.0417$) and a reduction in the incidence of constipation (0.24 ±0.43 vs. 0.47 ±0.51, $p = 0.0493$) were observed. A reduction in visceral sensitivity by butyrate was previously shown in a group of healthy volunteers. A double-blind, randomized, placebo-controlled crossover study was conducted in 11 healthy subjects who self-administered daily, before sleeping, rectal enemas containing 100 mmol/l butyrate in the first week, 50 mmol/l butyrate in the second week, and placebo (saline) in the third week. At the start and end of each test period, pain, urge, and discomfort were measured using a rectal barometer.

Administering butyrate at 50 mmol/l and 100 mmol/l respectively resulted in reductions in pain scores by 23.9% and 42.1% and discomfort scores by 44.2% and 69.0%, at a pressure of 4 mm Hg. At a higher pressure (67 mm Hg), butyrate decreased the pain scores by 23.8–42% and discomfort scores by 1.9–5.2% [15]. Colonic administration of butyrate at physiologically relevant concentrations was shown to dose-dependently decrease visceral sensitivity in healthy humans. Visceral hypersensitivity is thought to play a pivotal role in intestinal motor abnormalities and abdominal pain or discomfort; thus, butyric acid could be regarded as a potential solution in this issue.

The best-known mechanism of action of SCFA is the inhibition of proinflammatory mediator activities in the intestinal epithelium. In particular, butyric acid and its salts exert an anti-inflammatory effect. Sodium butyrate inhibits proinflammatory cytokine production by macrophages and monocytes, and reduces myeloperoxidase activity, primarily via inhibition of nuclear factor κB activation [16–18]. Evidence of the presence of low-grade inflammation in the intestinal mucosa of patients with IBS and some negative changes in their intestinal microflora were found [19, 20]. Increased myeloperoxidase activity in the large bowel was observed in adult patients with IBS [21]. Therefore, regarding the anti-inflammatory properties of butyric acid, a reduction in intestinal inflammation can result from butyric acid supplementation, which could potentially reduce difficulties in bowel movements.

Butyrate also supports mucosal barrier function by stimulating intestinal mucus production [22]. Butyric acid was documented to increase peristaltic efficiency by improving colonic smooth muscle contractility and regulating intestinal neurotransmission, especially in the case of slow peristalsis [23]. Moreover, all SCFAs limit the active secretion of water, sodium, and chloride ions by the intestinal epithelial cells [24]. These mechanisms of action of butyric acid seem to be useful in the treatment of defecation disorders.

So far, the main barriers in butyric acid application are its unpleasant taste and odour, and rapid absorption in the upper gastrointestinal tract, which makes it almost impossible to reach the large intestine. In Poland, microencapsulated sodium butyrate coated with triglyceride is currently available. This modern form of butyric acid, in contrast to its standard form, allows the delivery of active substances to the small intestine and colon. Most microgranules pass through the small intestine and then to the colon along with intestinal contents. Therefore, sodium butyrate is gradually released throughout the entire length of the small and large intestines.

However, despite all the cited potential mechanisms of action of butyric acid, the effectiveness of its supplementation in the treatment of constipation needs to be confirmed in well-conducted studies.

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