Butyric acid in irritable bowel syndrome

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Abstract

Butyric acid (butanoic acid) belongs to a group of short-chain fatty acids and is thought to play several beneficial roles in the gastrointestinal tract. Butyric anion is easily absorbed by enteric cells and used as a main source of energy. Moreover, butyric acid is an important regulator of colonocyte proliferation and apoptosis, gastrointestinal tract motility and bacterial microflora composition in addition to its involvement in many other processes including immunoregulation and anti-inflammatory activity. The pathogenesis of irritable bowel syndrome (IBS), the most commonly diagnosed functional gastrointestinal condition, is complex, and its precise mechanisms are still unclear. This article describes the potential benefits of butyric acid in IBS.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a functional bowel disorder that generates a significant health care burden and is the most commonly diagnosed functional gastrointestinal condition. Approximately 12% of adults in the general population experience symptoms of IBS [1, 2]. Several definitions of IBS exist. Table I shows the most commonly used diagnostic criteria, the so-called Rome III Criteria, for IBS in adults [3]. According to these criteria, IBS is classified into four subtypes based on predominant stool patterns, as shown in Table II. An American College of Gastroenterology position statement published in 2009 defines IBS as an abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least 3 months [4]. The pathophysiological mechanisms of IBS are still unknown. Brain–gut interactions, visceral hypersensitivity, abnormal motility, intestinal inflammation, post-infectious disturbances and alteration of microflora have all been suspected to play a role in the pathogenesis of this syndrome [5, 6]. Visceral hypersensitivity is believed to be a major contributing factor to abdominal pain in patients with IBS. Psychosocial factors seem to be also involved in the pathogenesis of IBS [7].

Irritable bowel syndrome management

Because the pathogenesis of IBS is unclear, treatment focuses on the relief of symptoms such as bloating, abdominal pain, diarrhoea and constipation. Treatment difficulties are increased by the heterogeneity of the IBS population (wide range of patient ages and complaints, varying degrees of symptom severity), lack of unequivocal treatment algorithms, and remarkably high placebo response rate with short-term trials reporting response rates of 16–71.4% [8]. Therefore, treatment strategies should be individualized with an emphasis on developing a good doctor-patient relationship. The management of IBS consists of changes in lifestyle, including eliminating high-gas foods such as carbonated beverages, salads, raw fruits and vegetables (especially cabbage, broccoli and cauliflower), and increasing physical activity. A high-fibre diet, as well as fibre supplements and osmotic laxatives that increase stool frequency are recommended for constipation-predominant IBS, while anti-diarrheal treatment is recommended for diarrhoea-predominant IBS. Moreover, various medications, including anticholinergics, antidepressants, antibiotics, simethicone and probiotics, have all been used in the treatment of IBS. The vast

Table I. Diagnostic criteria* for irritable bowel syndrome

Recurrent abdominal pain or discomfort** at least 3 days per month in the last 3 months associated with 2 or more of the following:
1. Improvement with defecation
2. Onset associated with a change in frequency of stools
3. Onset associated with a change in form (appearance) of stools

*Criteria fulfilled for the last 3 months with symptom/s onset at least 6 months prior to diagnosis
**Discomfort means an uncomfortable sensation not described as pain
In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 days a week during screening evaluation for subject eligibility.

Table II. Subtyping IBS by predominant stool pattern

1. IBS with constipation (IBS-C) – hard or lumpy stools ≥ 25% and loose (mushy) or watery stools < 25% of bowel movements

2. IBS with diarrhoea (IBS-D) – loose (mushy) or watery stools ≥ 25% and hard or lumpy stool < 25% of bowel movements

3. Mixed IBS (IBS-M) – hard or lumpy stools ≥ 25% and loose (mushy) or watery stools ≥ 25% of bowel movement

4. Unsubtyped IBS – insufficient abnormality of stool consistency to meet criteria for IBS-C, D or M

majority of these medications provide short-term relief, but evidence for their long-term efficacy has not been established. Evidence of the safety and tolerability of these drugs is limited. For all of these reasons, there is a great need for new IBS therapies.

Butyrates in the treatment of irritable bowel syndrome

Butyrates represent a potential new IBS therapy. To date, a few trials have been performed to evaluate the effectiveness of sodium butyrate on clinical symptoms and quality of life in patients with IBS. Banasiewicz *et al.* performed a double-blind, randomized, placebo-controlled study in which 66 adult patients with IBS received microcapsulated butyric acid at a dose of 300 mg per day or placebo as an adjunct to standard therapy. At four weeks, there was a statistically significant decrease in the frequency of abdominal pain during defecation in the butyric acid group ($p = 0.0032$). At 12 weeks, decreases in the frequency of spontaneous abdominal pain ($p = 0.0132$), postprandial abdominal pain ($p = 0.0031$), abdominal pain during defecation ($p = 0.0002$) and urge after defecation ($p = 0.0100$) were observed [9, 10]. In a preliminary report, Tarnowski *et al.* demonstrated an improvement of abdominal pain, abdominal discomfort and defecation rhythm in patients with IBS treated with microcapsulated sodium butyrate for 6 weeks, compared to those treated with placebo. In the same study, higher quality of life was noted in patients treated with butyrate [11]. It is worth noting that no side effects were observed during treatment with protected sodium butyrate, which confirms the safety of its use in clinical practice. Although the results of these two trials seem to be promising, the effectiveness of butyrate in the treatment of IBS needs to be confirmed. There is also a need for studies of the effectiveness of butyrate in children and adolescents.

Butyric acid

Butyric, acetic and propionic acids account for approximately 83% of the short-chain fatty acids (SCFAs) in the human colon [12]. The concentration of these acids in the intestinal lumen ranges from 60 mmol/kg to 150 mmol/kg [13], and the acetate-propionate-butyrate balance is relatively constant, with a typical ratio of 60 : 25 : 10 [14]. Short-chain fatty acids are rapidly absorbed by the epithelium of the gastrointestinal tract. In the large bowel, absorption reaches peak levels in the caecum and ascending colon by both active and passive transport [15, 16]. Production levels of butyric acid in the sigmoid colon and the rectum are low. Butyrate is the preferred energy source for colonic epithelial cells [17]. A well-balanced diet, rich in probiotics, prebiotics and fibre, is the preferred source of butyrate. Similarly to other SCFAs (acetic, propionic), endogenous butyric acid is produced by the bacterial fermentation of non-digestible carbohydrates and hexose oligomers with varying degrees of polymerization, such as non-starch polysaccharides, resistant starch, oligosaccharides (inulin and oligofructose), disaccharides (lactose) and sugar alcohols (sorbitol and mannitol) [13, 15]. Resistant starch has been found to be particularly butyrogenic. It occurs naturally in partially milled grains and seeds, uncooked potatoes, green bananas and various vegetables. The species of bacteria involved in the production of butyrate are *Clostridium* spp., *Eubacterium* spp., *Fusobacterium* spp., *Butyrivibrio* spp., *Megasphaera elsdenii*, *Mitsuokella multiacida*, *Roseburia intestinalis*, *Faecalibacterium prausnitzii* and *Eubacterium hallii* [18]. Recently, an increased intake of highly processed, low-fibre food products rich in simple sugars has been observed, resulting in low levels of butyrate production in the intestinal lumen. Therefore, butyrate supplementation potentially represents a good alternative to

dietary intake. Bird *et al.* documented an association between increased consumption of resistant starch and the amount of butyrate in faeces, and a lack of association with the incidence of diet-dependent disorders [19].

Pure butyric acid has an extremely pungent smell, which makes it very difficult to handle. It is quickly absorbed in the upper part of the gastrointestinal tract, which reduces its positive effects in the colon. These characteristics limit the clinical utility of pure butyric acid. Recently, a new range of products has been developed, in which butyric acid is encapsulated in a triglyceride matrix, resulting in slow release during its transport through the intestinal tract. Considering the potential pathophysiological factors involved in the aetiology of IBS, which include brain-intestine interactions, visceral hypersensitivity, abnormal motility, intestinal inflammation, post-infectious disturbances and alteration of microflora, in the next paragraph, we briefly summarize the possible mechanisms of action of butyrate that may be useful in the treatment of IBS.

Potential butyrate mechanisms of action

Butyratedirectly influences the gastrointestinal flora. The presence of butyrate-producing bacteria species suppresses the growth of *Escherichia coli, Campylobacter* spp.*, Salmonella* spp. and *Shigella* spp. [20]. Butyric acid may also play a beneficial role in the treatment of gastrointestinal infections. In experimental shigellosis, enteric supplementation of SCFAs reduced congestion, infiltration of inflammatory cells, and necrotizing features in the mucosa, which resulted in a reduced amount of faecal blood and mucus [21]. The efficacy of butyric acid in the prevention of water, sodium, chlorine and potassium loss confirms observations made in animals with cholera [22]. The fact that the passive absorption of water in the colon depends on the presence of SCFAs may explain the potential role of butyrate in clinical conditions involving diarrhoea [23]. The trophic effects of butyrate on intestinal cell proliferation have been demonstrated in animal models. Dietary supplementation with butyrate stimulated the elongation of the villi in the ileum and crypt depth in the caecum [24, 25]. Butyric acid has also been shown to exert potent anti-inflammatory effects both *in vitro* and *in vivo*. Its immunoregulatory and anti-inflammatory activity is presumably based on the topical inhibition of inflammatory mediators in the epithelium. The ability of butyrate to decrease concentrations of pro-inflammatory cytokines such as interleukin 8 (IL-8) and tumor necrosis factor-α (TNF-α) has been documented [26]. In mice, the intrarectal administration of butyric acid during an acute phase of experimental colitis attenuated intestinal inflammatory parameters [27]. Some anti-inflammatory effects of butyrate in the treatment of ulcerative colitis and radiation proctitis were also observed [28, 29]. The precise mechanisms underlying these effects have not been fully elucidated. The relief of abdominal pain seems to be a very important aspect of IBS treatment. Butyrate has a probable beneficial influence on the hypersensitivity of intestinal receptors, which results in a decrease of intraintestinal pressure. It improves bowel peristalsis and retractility of the circular muscle layer [9].

In summary, butyrate supplementation seems to be a promising therapy for IBS. However, data on its effectiveness are still very limited.

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