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
Diagnostic criteria* for irritable bowel syndrome

| Criteria fulfilled for the last 3 months with symptom/s onset at least 6 months prior to diagnosis |
|-----------------------------------------------|
| 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 |

*Discomfort means an uncomfortable sensation not described as pain
**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

Table II. Subtyping IBS by predominant stool pattern

| Subtyping IBS by predominant stool pattern |
|-------------------------------------------|
| 1. IBS with diarrhoea (IBS-D) – loose (mushy) or watery stools ≥ 25% of bowel movements |
| 2. Mixed IBS (IBS-M) – hard or lumpy stools ≥ 25% and loose (mushy) or watery stools < 25% of bowel movements |
| 3. IBS with constipation (IBS-C) – hard or lumpy stools ≥ 25% and loose (mushy) or watery stools < 25% of bowel movements |
| 4. Unsubtyped IBS – insufficient abnormality of stool consistency to meet criteria for IBS-C, D or M |

Butyric acid in irritable bowel syndrome

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 hexasaccharides 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., Butyribrio spp., Megaphera elsdenii, Mitsuokella multicaudata, 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...
dysregulation 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 reactivity 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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