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Exploring the Therapeutic Potential of Sodium Butyrate in Irritable Bowel Syndrome: A Literature Review

1. Nadia Miga-Orczykowska [NMO]
   https://orcid.org/0000-0002-0551-6159
   Stefan Wyszyński Provincial Specialist Hospital in Lublin, Aleja Kraśnicka 100, 20-718 Lublin, Poland
   nadmig98@gmail.com

2. Paulina Lemieszek [PL]
   https://orcid.org/0009-0001-6648-7283
   Stefan Wyszyński Provincial Specialist Hospital in Lublin, Aleja Kraśnicka 100, 20-718 Lublin, Poland
   paulina.lemieszek13@gmail.com

3. Ilona Sajkiewicz [IS]
   https://orcid.org/0009-0007-5954-3594
   Stefan Wyszyński Provincial Specialist Hospital in Lublin, Aleja Kraśnicka 100, 20-718 Lublin, Poland
   inasajka@gmail.com

4. Katarzyna Rudnicka [KR]
   https://orcid.org/0009-0005-6815-6276
   Stefan Wyszyński Provincial Specialist Hospital in Lublin, Aleja Kraśnicka 100, 20-718 Lublin, Poland
   katarzyna.rudnicka95@gmail.com

Review

Abstract

Introduction and purpose

Irritable bowel syndrome (IBS) is a prevalent digestive condition marked by symptoms like abdominal discomfort, bloating, and irregular bowel movements. Sodium butyrate, a short-chain fatty acid recognized for its anti-inflammatory effects and benefits to gut health, has gained attention as a potential treatment for IBS. This review seeks to assess the existing research on the effectiveness and safety of sodium butyrate in managing IBS.

Material and methods

This work was based on a review of the literature available on PubMed. We included studies corresponding to the keywords: sodium butyrate, irritable bowel disease, butyric acid.

Results

Research has shown that sodium butyrate supplementation significantly alleviated abdominal pain, bloating, and overall IBS symptoms compared to a placebo. Notable improvements were seen in both visceral pain sensitivity and gut permeability. Furthermore, combining sodium butyrate with probiotics may offer additional benefits. The treatment was generally well-tolerated, easily accessible, and cost-effective.

Conclusion

Sodium butyrate shows promise as a therapeutic option for managing IBS, with studies indicating its effectiveness in reducing symptoms and enhancing gut health. However, more extensive, well-structured clinical trials are required to validate these results, determine optimal dosage, and assess long-term safety and efficacy.

Keywords: sodium butyrate, irritable bowel syndrome, butyric acid

Introduction

Irritable bowel syndrome is a chronic condition of the small and large intestines classified as a functional gastrointestinal disorder. Irritable bowel syndrome is one of the most common gastrointestinal disorders worldwide. The prevalence varies depending on the population studied and the diagnostic criteria used. The condition is more common in women and young adults. [1] IBS most commonly presents as abdominal pain accompanied by bowel movement disturbances such as diarrhea, constipation, or alternating episodes of both. These symptoms negatively affect patients' quality of life. A significant percentage of patients may also experience co-occurring psychiatric disorders, such as depression or anxiety disorders. [2] IBS symptoms may suggest the presence of other gastrointestinal disorders or overlap with symptoms of other functional disorders, which can create diagnostic challenges. The condition is diagnosed based on the Rome IV criteria. Excluding organic disorders is essential for the diagnosis. [3] The etiology of the disease is not fully understood.

Important factors believed to predispose individuals to its development include disturbances in the gut-brain axis, gut dysbiosis, a history of infectious diarrhea, or heightened visceral sensitivity. [1] The treatment of IBS involves dietary management and symptomatic therapy. Scientific societies strongly recommend rifaximin and soluble fiber. In recent years, researchers have been highlighting the potential use of butyric acid, a naturally occurring short-chain fatty acid in the colon, for alleviating IBS symptoms. [4,5] The aim of this paper is to discuss the role of butyric acid in the treatment of IBS based on the available scientific literature.

Irritable bowel syndrome

IBS is a chronic disease of the small and large intestines, and it is the most common disorder of the gut-brain axis, which is currently replacing the previously used term "functional disorders." [6] It is estimated that the disease affects 10-20% of adults worldwide. Epidemiological data vary depending on the geographical region—IBS occurs with a prevalence of 1.1% in France and Iran, and up to 35% in Mexico. [1] The condition occurs approximately twice as often in women. Other data from Asia show that IBS occurs with a similar prevalence in both genders. [7] IBS is more common among younger individuals. Over half of the cases are diagnosed before the age of 35. Data suggest that the prevalence is higher among individuals with a high socio-economic status, which may support the involvement of psychological stress in the pathophysiology of the disease. [8] The frequency of IBS diagnosis is influenced by the diagnostic criteria used. Among the studied groups from the USA, Canada, and the United Kingdom, the prevalence of IBS was approximately twice as high using the Rome III Criteria compared to the prevalence using the Rome IV Criteria, which demonstrates that the currently accepted diagnostic criteria are more restrictive. [9] Increased risk of IBS has been observed in individuals with a positive family history. However, a more detailed analysis suggests that behavioral factors are more significant than genetic predispositions, as evidenced by the concordance of the condition in monozygotic twins being below 20%. [8]

Etiology

The etiology of the disease is not fully understood. Key factors in its pathogenesis include: disruptions in the brain-gut axis, which result in heightened visceral sensitivity or impaired gut motility.[10] The remaining etiological factors are disturbances in gut microbiota, past viral infections of the gastrointestinal tract, dysfunction of the immune system and the intestinal barrier. The development of IBS is likely due to the interplay of several of these abnormalities. The role of gut dysbiosis in the pathogenesis of IBS is supported by observed changes in gut microbiota composition in patients with this disorder. Studies show that stool samples from individuals with IBS have a lower proportion of bacteria from the genera *Bifidobacterium* and *Lactobacillus*, that are short-chain fatty acid producers, including butyric acid and an increased abundance of *Firmicutes* bacteria. [5,11]

Symptoms

The primary symptom of IBS is abdominal pain, which can be constant or intermittent and may occur periodically with the urge to have a bowel movement. It is most commonly located in the lower abdomen and the lower left quadrant.
According to the Rome IV criteria, IBS is diagnosed if abdominal pain persists for at least 3 months, occurring at least 1 day per week, and is associated with at least 2 of the following 3 features: related to the urge to have a bowel movement, a change in the frequency of bowel movements, or a change in the form of the stool. 4
IBS is classified into one of four types based on stool consistency according to the Bristol Stool Scale. The diarrhea (IBS-D) subtype is diagnosed when at least 25% of stools are rated as type 6 or 7, and less than 25% are rated as type 1 or 2. The constipation subtype (IBS-C) is identified when at least 25% of stools are type 1 or 2, and less than 25% are type 6 or 7. The mixed subtype (IBS-M) is characterized by more than 25% of stools being type 1 or 2 and simultaneously 25% of stools being type 6 or 7. The unclassified subtype includes the remaining cases. [2] Routine additional tests are not recommended to confirm IBS. In most cases, it is advised to perform a complete blood count, C-reactive protein, and stool calprotectin test. Depending on the symptoms, further diagnostic testing may include TSH (thyroid-stimulating hormone) levels or serological tests for celiac disease. Patients with alarm symptoms or those over 50 years of age should undergo a colonoscopy. [12]

Treatment

The treatment of IBS involves a combination of dietary changes, lifestyle modifications and medications tailored to symptoms (e.g., antispasmodics, laxatives, or antidiarrheals). Psychological therapies, probiotics, and in some cases, low-dose antidepressants, may also be used to manage symptoms. Treatment is personalized based on the type and severity of IBS symptoms. In the treatment of IBS-C, dietary modifications are considered, including increased intake of soluble fiber, which helps alleviate constipation. To manage constipation, linaclotide, a guanylate cyclase-C agonist, is used. It increases fluid secretion in the gastrointestinal tract, which accelerates bowel transit. It has also been proven to alleviate abdominal pain and bloating. 13 Another agent that increases secretion in the gastrointestinal tract is lubiprostone. It is effective in relieving constipation and associated symptoms like abdominal discomfort. [14] Macrogols are osmotically active agents with a proven laxative effect that are used in the treatment of constipation; however, there is no conclusive data on their effectiveness in alleviating IBS symptoms. They may serve as a supplementary therapy for patients with IBS-C. [4] In the diarrhea-predominant form, loperamide, an μ-opioid receptor agonist, is used. It slows intestinal transit and has proven effectiveness in alleviating diarrhea, but there is not enough evidence supporting its effect on IBS symptoms. Eluxadoline is a μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist as a result of which acts on the intestinal muscles while having limited side effects. Its effectiveness has been demonstrated in alleviating both diarrhea and visceral hypersensitivity. [12]
In patients with IBS without constipation, the use of the eubiotic rifaximin is recommended. It has been proven that a two-week therapy resulted in a reduction in the severity of bloating, abdominal pain, and diarrhea. [15] The basis for treating pain in IBS remains antispasmodic, such as hyoscine and drotaverine, which have anticholinergic effects. In the treatment of IBS,

tricyclic antidepressants and SSRIs have been used. They affect nerve conduction, which improves the functioning of the brain-gut axis. They are effective in alleviating overall IBS symptoms and pain, particularly chronic pain. [16]

In recent years, the significance of a low-FODMAP diet in managing IBS has been increasing. In a double-blind interventional study evaluating 20 patients with diarrhea-predominant or mixed-type IBS who followed a FODMAP diet, it was observed that after a three-week period of adherence, there was a reduction in the severity of all IBS symptoms. [17] Regarding dietary recommendations fiber plays a significant role in managing IBS, but its effectiveness depends on the type of fiber used.

Soluble fiber, such as psyllium, has been shown to be beneficial, especially for those with IBS-C. It helps to regulate bowel movements, can soften stools in constipation or add bulk in diarrhea. Studies have shown that soluble fiber can help reduce overall symptoms of IBS. Insoluble fiber (e.g., bran) is less effective and may even worsen symptoms in some IBS patients, especially those with IBS-D. This type of fiber can increase bloating, gas, and discomfort in sensitive individuals. [16]

Butyrate acid

Butyrate acid is one of the short-chain fatty acids (SCFAs). These are fatty acids with fewer than six carbon atoms produced primarily by the fermentation of dietary fibers by gut bacteria in the colon. Apart from butyrate, the most important SCFAs are acetate and propionate. Their concentration in the intestinal lumen typically ranges from 60 to 150 mmol/kg. The balance among these acids remains stable, with a typical ratio of 60:25:10 for acetate, propionate, and butyrate, respectively. They are quickly absorbed through nonionic diffusion and active transport, aiding in sodium and water absorption. Additionally, SCFAs, especially butyrate, promote the growth of beneficial bacteria like lactobacilli and *Bifidobacteria*. [18] Butyric acid plays a crucial role in maintaining gut health. It is the main energy source for colonocytes, helping to maintain the integrity of the gut lining. It has anti-inflammatory effects, reducing inflammation in the gut, enhances the production of mucus and tightens junctions between gut cells, preventing leaky gut and protecting against pathogens, influences gut motility, modulates immune responses in the gut. [19] Additionally, SCFAs, especially butyrate, promote the growth of beneficial bacteria like *Lactobacilli* and *Bifidobacteria*. [20]

Butyrate exhibits anti-inflammatory properties in intestinal diseases. A study assessed the effect of butyric acid on gut microbiota composition in patients with inflammatory bowel diseases. In 19 Crohn's disease patients and 30 ulcerative colitis patients, oral supplementation of sodium butyrate or placebo alongside standard therapy was administered for 2 months. A novel lipophilic microcapsule formula was used, enabling substance delivery to the distal colon. Results showed increased butyrate-producing Butyricicoccus in Crohn's patients and short-chain fatty acid-producing Lachnospiraceae in ulcerative colitis patients. [19]Scientists conducted a study to evaluate whether sodium butyrate and inulin can alleviate obesity-induced gut barrier dysfunction. The research was performed on mice with diet-induced obesity through a Western diet. The mice were then supplemented with 10% inulin and 5% sodium butyrate for 12 weeks. Western-style diet (WSD)-induced obesity in mice led to elevated urinary claudin-3 levels, indicating compromised tight junctions. Inulin and

sodium butyrate supplementation significantly reduced these levels. Additionally, WSD increased intestinal permeability, as shown by higher absorption of a polyethylene glycol marker.

However, inulin and sodium butyrate supplementation decreased this permeability, suggesting that these supplements help reinforce the intestinal epithelial barrier. Their findings suggest that inulin and sodium butyrate help restore the integrity of the colonic tight junction barrier. [21]

Therapeutic Potential of Sodium Butyrate in Managing IBS Symptoms

In recent years, scientists have been closely exploring the potential of sodium butyrate in alleviating IBS symptoms. Research findings provide evidence supporting its effectiveness in this area.

Polish researchers evaluated the effectiveness of sodium butyrate in a triglyceride matrix for alleviating symptoms and improving quality of life in a sample of 3,000 IBS patients. The study included individuals aged 18 and older who met the Rome IV criteria for IBS diagnosis. The most common IBS types were mixed (39%), diarrhea-predominant (29%), and constipation-predominant (21%). After 12 weeks of supplementation 150 mg of sodium butyrate twice daily, significant symptom improvements were reported, including reduced bloating, abdominal pain, diarrhea, and constipation. The treatment was well-tolerated, with 93.9% of participants expressing willingness to continue. [22]

In a double-blind, randomized, placebo-controlled study, 66 patients were randomized to two groups: one receiving 150 mg of microencapsulated sodium butyrate twice daily and the other receiving a placebo. The study included patients who experienced IBS symptoms despite undergoing therapy for the past 3 months and continued their existing treatment throughout the duration of the experiment. Patients assessed gastrointestinal symptoms using the VAS-IBS scale before starting the study and during follow-up visits. After 4 weeks, the group receiving sodium butyrate showed a statistically significant improvement in abdominal pain associated with defecation. After 12 weeks, this group exhibited a statistically significant improvement in spontaneous abdominal pain, abdominal pain during defecation, urgent bowel movements, and constipation. After 12 weeks of sodium butyrate supplementation, 53% of the participants responded positively to the closed question about noticing a subjective difference in IBS symptoms, compared to 15.6% of patients receiving a placebo. [23]

In a study conducted on rat models of irritable bowel syndrome (IBS), visceral allodynia and gut hyperpermeability were induced by lipopolysaccharide (LPS) or repeated water avoidance stress (WAS), involving corticotropin-releasing factor (CRF) and proinflammatory cytokines. Sodium butyrate was tested for its potential to alleviate these symptoms. Administration of sodium butyrate for 3 days effectively reduced LPS-induced visceral pain and gut permeability in a dose-dependent manner. It also blocked the effects of repeated WAS and CRF. [24]

The researchers designed a new study to investigate the effects of 12 weeks of supplementation with microencapsulated sodium butyrate at a dose of 300 mg, combined with probiotics containing Lactobacillus and Bifidobacterium strains, in patients with IBS, compared to a control group receiving a placebo. Patients will be evaluated using the BS-

Severity Scoring System (IBS-SSS), IBS-Global Improvement Scale (IBS-GIS), IBS-Adequate Relief (IBS-AR), and IBS-QOL after 12 weeks. The study results will provide valuable information on the use of sodium butyrate in combination with probiotics for this patient group. [5]

Conclusion

The use of sodium butyrate in patients with irritable bowel syndrome (IBS) shows promising potential for symptom relief and improvement in quality of life. Preclinical studies have demonstrated that sodium butyrate effectively reduces visceral pain and gut hyperpermeability, both of which are common issues in IBS. Clinical trials further suggest that sodium butyrate can lead to significant improvements in IBS symptoms, such as abdominal pain and overall gut health. The beneficial effects appear to be mediated through various pathways, including anti-inflammatory mechanisms and modulation of gut permeability. Continued research is essential to fully elucidate its efficacy, optimal dosing, and long-term benefits in diverse patient populations.

Disclousure:

Authors' contribution:

Conceptualization: Nadia Miga-Orczykowska
Methodology: Katarzyna Rudnicka, Ilona Sajkiewicz
Software: Katarzyna Rudnicka
Check: Paulina Lemieszek, Ilona Sajkiewicz
Formal analysis: Nadia Miga-Orczykowska
Investigation: Katarzyna Rudnicka, Ilona Sajkiewicz
Resources: Nadia Miga-Orczykowska, Paulina Lemieszek
Data curation: Paulina Lemieszek
Writing-Rough Preparation: Nadia Miga-Orczykowska, Ilona Sajkiewicz
Writing-Review and Editing: Paulina Lemieszek, Katarzyna Rudnicka
Visualization: Katarzyna Rudnicka, Ilona Sajkiewicz
Supervision: Nadia Miga-Orczykowska
Project Administration: Paulina Lemieszek

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