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Short-chain fatty acids and their impact on human health – a review

Krótkołańcuchowe kwasy tłuszczowe i ich wpływ na zdrowie człowieka – artykuł przeglądowy

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Abstract

Introduction and Objective. Short-chain fatty acids (SCFA) are substances that are naturally produced and metabolised in the human body. They exert many beneficial effects on the system and could help treat many diseases. This paper reviews the current state of knowledge on SCFA, analysing their production, mechanism of action and potential use in medicine.
Review Methods. The review is based on an analysis of literature available in the PubMed database using the key words: ‹short-chain fatty acids, ‹gut microbiome›, ‹butyrate›.
Brief description of the state of knowledge. Short-chain fatty acids are common substances produced by commensal bacteria residing in the large intestine. Three major SCFA are: butyrate, propionate and acetate, products of bacterial metabolism of dietary fibre that naturally occur in the gastrointestinal tract. SCFA have anti-inflammatory properties, modulate the gut microbiota and the immune system, help maintain the health of the gut, including the integrity of the intestinal epithelial barrier. Many attempts have been made to incorporate SCFA into the treatment of various diseases, and few adverse effects have been documented. The studies primarily focused on diet interventions with dietary fiber, probiotics and fermented foods containing SCFA. Promising results have been observed regarding, *inter alia,* the therapy of obesity, diabetes, inflammatory bowel diseases, lipid disorders and cardiovascular diseases.
Summary. Short-chain fatty acids are vital for the mainteance of human health. Their unique bioactivity, natural occurrence and safety could potentially lead to their wider application in medicine.

Key words

short-chain fatty acids, gut microbiome, butyrate

Streszczenie

Wprowadzenie i cel pracy. Krótkołańcuchowe kwasy tłuszczowe (ang. *short-chain fatty acids*, SCFA) to substancje, które są naturalnie wytwarzane i metabolizowane w organizmie człowieka. Niosą one liczne korzystne dla organizmu skutki i mogą wspomóc leczenie wielu chorób. W niniejszym artykule dokonano przeglądu aktualnego stanu wiedzy na temat SCFA, analizując ich produkcję, mechanizm działania i potencjalne zastosowanie w medycynie.
Metody przeglądu. Niniejsza praca bazuje na analizie literatury dostępnej w bazie danych PubMed. Wykorzystane do przeglądu artykuły wyselekcjonowano z użyciem następujących słów kluczowych: „krótkołańcuchowe kwasy tłuszczowe", „mikrobiom jelit", „maślan".
Opis stanu wiedzy. Krótkołańcuchowe kwasy tłuszczowe są substancjami wytwarzanymi przez bakterie komensalne zamieszkujące jelito grube. Trzy główne SCFA to: maślan, propionian i octan. Są one produktami zachodzącego w przewodzie pokarmowym bakteryjnego metabolizmu błonnika pokarmowego. SCFA mają właściwości przeciwzapalne, modulują mikrobiotę jelitową i układ odpornościowy, pomagają utrzymać zdrowie jelit, w tym integralność bariery nabłonkowej jelit. Podjęto wiele prób zastosowania SCFA do leczenia różnych chorób, przy czym stwierdzono nieliczne działania niepożądane. Badania opierały się głównie na interwencjach dietetycznych, polegających na dostarczaniu błonnika, probiotyków i sfermentowanej żywności zawierającej SCFA. Obiecujące wyniki zaobserwowano w odniesieniu do terapii otyłości, cukrzycy, chorób zapalnych jelit, zaburzeń lipidowych i chorób sercowo-naczyniowych.
Podsumowanie. Podsumowując, SCFA są niezbędne dla utrzymania ludzkiego zdrowia. Ich unikalna bioaktywność, naturalne występowanie i bezpieczeństwo mogą prowadzić do ich szerszego zastosowania w medycynie.

Słowa kluczowe

krótkołańcuchowe kwasy tłuszczowe, mikrobiom jelit, maślan

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INTRODUCTION

Short-chain fatty acids (SCFA, SCFAs) are common, small, 2–4 carbon chain substances. They are the primary metabolites of carbohydrate fermentation by anaerobic bacteria. These reactions take place in the large intestine, where three major SCFAs: butyrate, acetate and propionate, are synthesised from dietary fibre [1] in different metabolic pathways by heterodox bacteria [2]. These molecules play various roles in maintaining the body's health. SCFAs activity is necessary for sustaining the proper functioning of the gut, and through their unique qualities they modulate the metabolism of the entire system through a range of tissue-specific mechanisms [3]. Examples of the characteristics of these substances are anti-inflammatory and immunomodulatory properties [4]. The most important, although not the only factor for maintaining a normal, favourable concentration of SCFA, is the diet, which directly affects the gut microbiome [5, 6]. This aim of the review is to analyse the latest scientific reports on short-chain fatty acids and their impact on human health, as well as the potential for using SCFA in medicine.

REVIEW METHODS

The review is based on complete original papers, meta-analyses and review articles in English only, and available in the PubMed database using the key words: ‹short-chain fatty acids, ‹gut microbiome›, ‹butyrate›, which were used in order to find articles specific to short-chain fatty acids and their relation to gut microbiome, with an emphasis on butyrate- the most important SCFA. Literature published between 2015–2024 were used, of which 87.8% had been published between 2020–2024.

STATE OF KNOWLEGE

Pharmacokinetics and pharmacodynamics of SCFA- an overview. Short-chain fatty acids are synthesised by bacteria which inhabit the large intestine through the anaerobic fermentation of dietary fibre – mainly starch, pectins, celulose, hemicellulose and fructans. The concentration of SCFA decreases with the length of the colon [2] and with age [7]. Over 90% of SCFA are absorbed from the intestinal cavity and metabolised in liver [4], prior to which, however, SCFAs are taken up by colonocytes and stimulate Na^+-dependent fluid absorption [8].

Butyrate is the main source of energy for colonocytes and plays a significant role in maintaining the integrity and optimal permeability of the intestinal barrier[9]. Due to their intensive use by intestinal cells, only small amounts reach the liver. On the other hand, acetate and propionate reach the liver in larger quanities through the portal vein, where about 40% of acetate and 80% of propionate are metabolised. Very little SCFA bypasses the hepatic circulation and enters directly into the systemic circulation through internal iliac vein [4].

A trial conducted by Gill et al. demonstrated, that fermented foods, such as apple cider, kombucha, kimchi and soft cheese are a natural good source of short-chain fatty acids that have a beneficial effect on microbiota of the host gut [1].

Properties of SCFA. The intestinal epithelial barrier(IEB) is an intermediary between the external and internal environment of the body, and plays a key role in protection against pathogens and harmful antigens. The IEB is formed by the mucus layer, the lamina propria of the mucosa and epithelial cells. Leukocytes, the intestinal microbiota and antimicrobial peptides are important factors in maintaining the proper function of this barrier [10, 11]. A key feature of the intestinal barrier is its selective permeability to various components of ingested food. This is mainly achieved by epithelial cells, which are linked by peptide complexes – tight junctions (TJs) and adherens junctions. TJs provide selective control of molecules and ions transported via the paracellular pathway, thus influencing the integrity of the epithelial barrier [11, 12].

Beneath the intestinal epithelium lies the lamina propria consisting of immune cells, such as neutrophils, macrophages, mast cells and lymphocytes. These cells, in response to antigenic stimulation from pathogens or other particles of the food mixture, proceed to fight off potential threat, and in the process may directly affect enterocytes by damaging them, causing IEB dysfunction [13, 14]. Fortunately, the intestinal microbiota, through the production of SCFA, supports maintenance the continuity of the intestinal barrier. Short-chain fatty acids induce increased expression of tight junctions forming proteins, supporting the preservation of physiological epithelial polarity and assist the first line of defence against pathogens by regulating AMP synthesis [9].

A number of studies show that the SCFA content of faecal and saliva samples is markedly reduced in people with active inflammatory gastrointestinal diseases [9, 15], such as inflammatory bowel diseases (IBD) [9, 16]. The exacerbation of symptoms of autoimmune diseases is due, among other things, to the dysfunction of regulatory T cells, leading to an increase in chronic inflammatory processes which are inhibited by SCFA [17]. Inhibition of inflammation may occur through G-protein coupled receptors, leading to the activation of signalling molecular cascades that control the immune functions of the cell [9]. Gill et al. conducted a study which demonstrated that SCFA supplementation led to changes in lymphocyte subsets distribution, with a lower abundance of MAITs, Th1 cells and naïve B cells in peripheral blood [18]. Butyrate and propionate also affect the secretion of pro-inflammatory cytokines. They inhibit the production of IL-6 and reactive oxygen species as well as enhance the expression of anti-inflammatory IL-10. Acetate attenuates neutrophilic inflammation by decreasing nuclear factor-kappa B activity, and enhancing the synthesis of anti-inflammatory IL-10 and annexin A1, transforming growth factor-β. SCFA also protect cells from an excessive inflammatory response induced by lipopolysaccharide. There is also evidence of acetate negatively correlating with the pro-inflammatory interferon-γ [4, 19]. Immunomodulatory properties could potentially be used to support the treatment of non-gastrointestinal immune-mediated diseases, including, but not limited to, diabetes, rheumatoid arthritis and multiple sclerosis [20].

An important aspect of the activity of SCFAs is the effect on tissue energy metabolism by the regulation of appetite. Butyrate has been found to exert an anorexigenic effect through an activation of vagal afferent neurons and their projection sites. Acetate and propionate affect the serum level of glucagon-like peptide 1, peptide YY and leptin which signal satiety to the appetite centre of the brain. All SCFAs impact appetite through modulation of genes and hormones, namely, tumour necrosis factor receptor superfamily member 9, cytochrome-C oxidase IV, mitochondrial transcription factor A, and free fatty acid receptor 2. It has also been suggested, that SCFA may inhibit lipogenesis and triglyceryde accumulation, thereby ameliorating metabolic disturbances associated with obesity. Acetate additionally promotes the browning of white adipose tissue which, by increasing thermogenesis, could lead to the reduction of body adiposity [4, 21]. A recent meta-analysis has also shown that SCFA may positively impact fasting insulin level in insulin-resistant patients [22].

Animal studies suggest that a prebiotic diet may positively impact brain function through the gut-brain axis. Medawar et al. conducted a randomised clinical trial aimed at assessing the correlation between diet and food decision making in adults. The participants supplemented inulin, which is known to affect SCFA concentration, for 14 days; SCFA, hormones, glucose/lipid and inflammatory markers were measured in fasting blood. Microbiota and SCFA in stool were also assayed. Participants, compared with placebo, showed decreased brain activation towards high-caloric wanted food stimuli in the bain. Moreover the data showed a significant increase of SCFA-producing *Bifidobacteriaceae* and changes in *Actinobacteria* abundance, previously linked with SCFA production. This study indicates that, among other factors, SCFAs may play a part in reward-related brain activation during food-decision making [23, 24].

Diet and gut microbiome. The gut microbiome consists of a heterogenous community of microbes: bacteria, fungi and protozoa. The most abundant bacterial phyla inhabiting the gut are *Firmicutes, Bacteroides, Actinomycetes, Proteobacteria and Verrucomicrobia,* with 90% of the gut microbiota being represented by *Bacteroides and Firmicutes.* Maintaining a proper composition and diversity of the gut microbiota is necessary for preserving the well-being of the entire system. The role of bacteria in supporting human health is to assist with the digestion and absorption of nutrients, prevent the proliferation of pathogenic bacteria, maintain the intestinal barrier, and regulate the gut-brain axis and the immune system, as well as produce beneficial substances – such as SCFAs [25]. The SCFA producing bacteria are, *inter alia: Akkermansia spp., Faecalibacterium prausnitzii, Roseburia spp., Bifidobacterium spp., Ruminococcus spp.* and *Turicibacter spp* [6, 21, 23, 26, 27]. The composition of the intestinal microbiota is influenced by a number of factors, e.g. chronic diseases (diabetes, obesity), antibiotic therapy, aging, diet, intake of probiotics and prebiotics, etc[8, 26, 28, 29]. An indicator of healthy gut microbiota is the relative amount of butyrate; in simple terms, the more butyrate, the better [30].

As mentioned earlier, diet is an extremely important factor for maintaining an optimal concentration of short-chain fatty acids in the digestive tract. There are a number of interrelationships between the food consumed, the gut microbiota and SCFA [31]. The food consumed is the main source of fermentable substrates, as it has direct impact on gut microbiota fermentation rate and the production of metabolites. The primary way to stimulate SCFA production by bacteria is to provide them with the necessary substrates- non-digestible carbohydrates – dietary fibre [32]. An insufficient intake of fibre can lead to a reduction in microbiota biodiversity and reduced SCFA production due to a shift towards utilisation of dietary and endogenous protein sources by gut bacteria. According to a study, dietary fibre supplementation significantly affects the abundance of acetate-producing *Bifidobacterium spp.* An overall increase in SCFA concentration is observed, with acetate and propionate production significantly increasing [33]. Worthy of special attention is the Mediterranean diet – a diet rich in legumes, nuts and fruits, which are sources of oligosaccharides, polyols and water-insoluble fibre-cellulose. These foods play a significant role in the health benefits associated with SCFAs [34]. In order to increase the concentration of SCFA in the large intestine, supplements that directly deliver specific acids to the digestive tract can also be used. In research, both vinegar (source of acetate) and sodium butyrate are utilised, and is a simple way of supplying these substances without causing any adverse effects [18, 35]. Delivery of SCFA through an intake of fermented food seems to be a cost-effective and accessible method. A chromatographic study of commonly consumed foods and beverages showed that apple cider vinegar, white wine, pickled vegetables (onions, gherkins), cheese (blue vein, brie), kombucha and Greek yoghurt are very good sources of SCFA (Tab. 1). Consumption of these products may have beneficial therapeutic benefits if delivered over a longer period of time for a metabolic effect to occur [1].

Table 1. Example foods and beverages and their contents of SCFAs[1]

Food/beverage	Serving size	Contents of short-chain fatty acids (mg per serve)		
		Acetate	*Propionate*	*Butyrate*
Apple cider vinegar	15g	1,015.82	4.05	3.42
White wine vinegar	15g	1,017.73	0.00	0.00
Pickled onion	30g	723.30	5.10	12.81
Gherkin	40g	872.08	26.00	21.24
Blue vein cheese	25g	32.93	0.00	136.54
Brie cheese	25g	8.30	0.00	105.91
Kombucha	330g	1,225.95	0.00	0.00
Greek style yoghurt	100g	15.19	0.00	3.28

Use of SCFA in medicine. The unique properties of SCFAs have prompted scientists to investigate the potential use of these compounds in the treatment of diseases. It was observed that the treatment of diabetic mice with SCFA induced a reduction in blood glucose and lipids. A meta-analysis by Zheng et al. showed that a similar correlation could be observed in humans. They analysed 18 human studies, which concluded that each of the short-chain fatty acids had an effect on lowering fasting glycaemia compared to control groups, but the most effective intervention was butyrate therapy. In addition, acetate and propionate showed cholesterol- and triglyceride-lowering effects [36]. An impact of SCFA on glycated haemoglobin level in patients with type 2 diabetes has also been noted [33].

Modulation of the gut microbiota may be useful in the treatment of lipid disorders. Xu et al. conducted a trial analysing the effects of oat consumption on the microbiome and SCFA. This intervention resulted in an increase in the abundance of beneficial bacteria, including SCFA producers. Concomitantly, the levels of triglycerides and LDL cholesterol were reduced [37].

Short-chain fatty acids could also protect the bone mineral density (BMD) of patients undergoing weight-loss dietary treatments. A study by Zhou et al. found that dietary fibre intake, correlating positively with SCFA concentration, expediently influenced the BMD of individuals struggling with obesity. Butyrate-related genetic variants, which differentiated the participants, were also confirmed to play a large role [38]. All in all, studies show that dietary interventions and probiotic intake may be a potential strategy in fighting obesity, diabetes and lipid disorders[5].

Data from the SPIRIT (Survivorship Promotion In Reducing IGF-1 Trial) which studied weight-loss intervention among 121 adult cancer survivors, supports the theory of SCFA impacting high blood pressure. A 12-month observation showed that baseline serum and faecal butyrate levels inversely correlated with hypertension. Moreover, an increase in both serum and faecal butyrate was associated with decreased systolic and diastolic pressure. This shows that butyrate might be a beneficial addition to the treatment of high blood pressure alongside conventional therapy [39]. Studies also show that most SCFA exert positive effects on cardiovascular diseases. Butyrate and propionate are stated to reduce the risk of coronary artery disease and atherosclerosis. Acetate can also affect hypertension and prevent atherosclerosis. These effects are primarily related to SCFA's anti-inflammatory, immunomodulatory and several neurohumoural regulatory properties [2].

The gastrointestinal tract is the organ system most heavily exposed to the effects of short-chain fatty acids, with SCFAs keeping the IEB intact and preventing many inflammatory bowel diseases [12]. In the course of bowel diseases, the gut microbiota becomes disrupted, with changes in diversity and microbial composition. This may lead to the increase of inflammation and consequently, an exacerbation of clinical symptoms. Studies show that SCFA can modulate the microbiome by shifting it towards beneficial bacteria that exert an anti-inflammatory effect on the gut. This leads to alleviation of the disease and partially prevents future onsets of symptoms [16]. Trials suggest that the use of prebiotics supporting SCFA-producing bacteria, as well as the intake of probiotics containing these bacterial strains, can alleviate the symptoms of chronic constipation and functional dyspepsia [26, 40]. Importantly, a recently performed meta-analysis proved that SCFA have anti-cancer properties. Researchers found that lower concentration of the three major SCFAs: acetate, propionate and butyrate, is associated with a higher risk and incidence of colorectal cancer.

To sum up, studies show that diet, microbiota and SCFA, have a tremendous impact on the health of the gut and must be taken into account in the prevention, diagnosis and treatment of gastrointestinal diseases [41].

CONCLUSIONS

Short-chain fatty acids are simple compounds naturally occurring in the human body due to the microbiota. Diet is the most important factor on which their concentration depends, particularly the supply of dietary fibre, which is the primary substrate for the synthesis of SCFAs by bacteria. The supply of probiotics is also important, as well as the SCFA themselves from fermented products. SCFA exhibit a number of beneficial molecular properties for human health. They have anti-inflammatory and immunomodulatory effects, influence the composition of the intestinal microbiome, maintain the function of the intestinal epithelial cells, including the efficiency of the intestinal barrier, regulate blood glucose and lipid levels, and have anti-cancer activity.

The unique properties of SCFA have the potential to be utilised in the treatment of many diseases. Studies show their potential in supporting the treatment of obesity, inflammatory bowel disease and diabetes, as well as metabolic and cardiovascular diseases. An advantageous aspect of SCFA in medicine is their safety profile, as they cause few to no side-effects. Whether SCFA will find use as components in conventional therapies depends on a better understanding of them; therefore, it is still important to carry out studies that focus primarily on their points of entry.

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