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Sodium Butyrate as Gut Microbiota Modulators: Mechanisms of Action and Potential Clinical Applications - Literature Review and New Perspectives

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Abstract

Introduction

Sodium butyrate is an organic chemical compound belonging to sodium salts, which has the potential to be used in anticancer therapy. It reduces inflammation of the intestinal mucosa and promotes the development of beneficial intestinal flora, thanks to which it helps maintain homeostasis. Therefore, butyrate reduces the risk of developing colon cancer or reverses pathological changes occurring under the influence of this cancer. Scientific studies have also shown a beneficial effect of butyrate on the side effects of anticancer treatment - chemotherapy and radiotherapy. A proper diet also has a beneficial effect on the production of endogenous butyrate and reduces the risk of developing colon cancer. It is recommended to use a Mediterranean diet, rich in dietary fiber, highly unsaturated fatty acids and fresh vegetables and fruits. It is recommended to avoid highly processed products, rich in simple sugars and saturated fatty acids, and to limit the consumption of red meat.

Materials and methods

This article is based on the literature found in the PubMed and other scientific databases from the period of 1978-2023 with the use of key words such as “butyrate” “sodium butyrate” “colon cancer” “anticancer treatment” “intestinal microbiota” “Mediterranean diet”.

Conclusion

Sodium butyrate is a potential substance that, through its properties, may support the treatment of colorectal cancer. Additionally, the use of an appropriate diet has a positive effect on the intestinal microflora, allowing the action of sodium butyrate and reducing the risk of colorectal cancer.

Keywords: butyrate, sodium butyrate, colon cancer, anticancer treatment

Introduction

Sodium butyrate is an organic chemical compound (sodium salt) formed by replacing the proton of the carboxyl group of butyric acid with a sodium ion. It acts as a histone deacetylase inhibitor and geroprotector. Sodium butyrate is a salt with potential anti-cancer properties.[1] Butyrate, a short-chain fatty acid, competitively binds to the zinc sites of class I and II histone deacetylases (HDACs).[2] This binding affects the hyperacetylation of histones, which results in a modified DNA conformation, which in turn leads to the unfolding or loosening of chromatin. Increased chromatin accessibility to transcription regulatory complexes leads to increased transcriptional activation of various epigenetically suppressed genes. Butyrate, an HDAC inhibitor, induces cell cycle arrest in G1 or G2/M and also increases the expression of other genes and proteins involved in cellular differentiation and apoptotic signaling.[3] As a geroprotector, sodium butyrate is a senotherapeutic agent that aims to target the root cause of aging and age-related diseases.[4] Butyrate is produced by the fermentation of undigested dietary fiber and is a promising candidate for the treatment of cancer.[5] However, the mechanism underlying sodium butyrate-induced autophagy in colorectal cancer is not yet completely understood.

Colorectal cancer (CRC) poses a significant burden to society and its incidence remains consistently high.[6] The mortality rate in colorectal cancer has been decreasing in recent years

thanks to the improvement of modern technologies for examining the digestive tract and the strengthening of patients' health awareness.[7] The mechanism of CRC is complex and multifactorial, related to excessive immune activation, individual genetics, treatment used in a given patient and an incorrect lifestyle.[8]

Sodium butyrate and the immune system

Butyrate is known as one of the most important metabolites produced by bacterial fermentation in the intestines. Butyrate biosynthesis takes place via two metabolic pathways. The first one concerns the phosphorylation of butyryl-CoA to butyryl phosphate, and then the transformation to butyrate with the participation of the enzyme - butyrate kinase. The second metabolic pathway concerns the transformation of butyryl-CoA into acetate and then the transformation into butyric acid.[9] Its impact on the immune system is related to, among others, with the regulation of the expression of pro- and anti-inflammatory mediators. Butyrate inhibits the expression of pro-inflammatory IL-1b and IL-6, while stimulating the expression of the anti-inflammatory cytokine IL-10.[10] Also, butyrate supports anti-cancer immunity by influencing the activity of CD8+ T lymphocytes.[11] Butyrate provides anti-inflammatory effects and increases apoptosis in cancer cells.[12] Moreover, it affects the immunity of the mucous membranes and maintains the stability of the intestinal microflora, leading to homeostasis.[13]

Maintaining the integrity of the intestinal mucosa and sodium butyrate

G protein-coupled receptors (GPCRs) exist in epithelial cells and are the receptor for butyrate.[14] The attachment of butyrate to GPCR receptors influences the modulation of cellular functions in many tissues and cells, such as: B and T lymphocytes, neutrophils, adipose tissue and colon myeloid cells.[15] Butyrate stimulates the proliferation of epithelial cells and the production of the mucous layer, which contributes to improving the tightness of the intestinal barrier.[16] An important part of membrane proteins is the claudin family, which is responsible for maintaining tight intercellular connections. Butyrate increases claudin-1 expression; therefore, it is important in the context of maintaining the integrity of the intestinal barrier.[17] Furthermore, butyrate increases the expression of the MUC2 gene, thereby promoting the synthesis of mucins that protect epithelial cells against the harmful effects of toxins.[18] Taking into account the above facts, it can be concluded that butyrate is an essential

metabolite influencing the function of the intestinal barrier, which seems to be necessary for patients suffering from colorectal cancer, in whom increased destruction and disruption of the integrity of the intestinal barrier is observed.

The influence of diet on butyrate availability and the development of colorectal cancer

Consuming large amounts of saturated fatty acids, simple sugars and highly processed food is one of the biggest problems of the modern world.[19] Such a diet negatively affects the intestinal microbiome, leading to the growth of undesirable, opportunistic bacterial colonies, the development of inflammation of the mucous membranes and a reduction in the production of SCFAs (including butyrate).[20] Studies have shown that the above changes can be inhibited by butyrate supplementation. The number of butyrate-producing bacteria may increase after administration of omega-3 fatty acids and docosahexaenoic acid (DHA).[21] In the work of Zhuang et al. It has been shown that both EPA and DHA contribute to the growth of butyrate-producing bacterial colonies, while reducing the number of bacteria that negatively affect the intestinal mucosa.[22] As can be seen from the above, omega-3 fatty acids have a beneficial effect on the composition of the intestinal microflora, improve the integrity of the intestinal barrier and reduce the number of unfavorable intestinal bacteria. A proper diet has one of the key roles in the prevention of colorectal cancer. Consuming large amounts of red and heavily processed meat, a diet high in saturated fat, low in fiber and fresh vegetables and fruit increases the risk of developing colorectal cancer. According to research, dairy products are believed to protect against CRC due to their high content of calcium, vitamin D, conjugated linoleic acid, butyric acid and fermented dairy products. Ionized calcium can form insoluble soaps with free fatty acids and bile acids, which promote the development of cancer. This has led to the hypothesis that calcium has anti-cancer effects and protects against CRC.[23] Observational and laboratory studies provide compelling evidence that diet has the potential to modify the incidence of CRC. It is recommended to use a Mediterranean diet, which is rich in food with a high content of dietary fiber, highly unsaturated fatty acids and fresh vegetables and fruits, which leads to the development of proper intestinal microbiota and maintains intestinal homeostasis.[24]

Butyrate-induced cancer cell apoptosis

Butyrate can induce apoptosis of colorectal cancer cells.[25] According to research conducted by Kang et al., it was shown that the use of sodium butyrate has a positive effect on the elimination of colorectal cancer by reducing the thickening of the intestinal walls, and the degree of erosions, ulcers, bleeding and inflammation were significantly alleviated.[26] This contributed to a decrease in the number of colorectal cancers. The anticancer effect of butyrate on colon cancer cells (SW480) was also confirmed in the work of Elimrani et al. test.[27] Summarizing the above research results, it can be assumed that butyrate has the ability to prevent and weaken the progression of colorectal cancer.

Impact on anticancer treatment

Studies have shown that butyrate has a stimulating effect on the action of 5-fluorouracil on cancer cells during chemotherapy.[28] Additionally, nearly 40% of patients treated with chemotherapy developed inflammation of the intestinal mucosa. The use of butyrate may reduce the side effects of chemotherapy treatment by rebuilding and protecting the intestinal mucosa.[29] Butyrate has also been shown to improve effectiveness of radiotherapy.[30] In a study by Kang et al., it was proven that colon cancer leads to a change in the composition of the intestinal microbiota, which promotes the destruction of the mucous membrane and the development of pathology.[31] The use of butyrate allows for the restoration of normal intestinal microbiota and the reduction of pathological changes in the intestinal mucosa.[32] During the development of colorectal cancer, tumors destroy the normal intestinal microecosystem, leading to the formation of pathological intestinal flora, producing toxic substances that disrupt the intestinal barrier and exacerbate the development of cancer.[33] CRC stimulates the growth of toxic Verrucomicrobiales colonies, but also promotes the enrichment of the flora with Lactobacillales and Enterobacterales bacteria, which leads to damage to the intestinal mucosa.[34] The use of butyrate effectively prevents the population growth of these colonies and facilitates the development of beneficial bacteria.[35] Bifidobacteria are key symbiotic bacteria found in the intestine that enhance the intestinal barrier function and have a beneficial effect on inhibiting cancer and inflammation.[36] The introduction of butyrate in the treatment of CRC will lead to the rebirth of the Bifidobacterium population.[37] Therefore, butyrate inhibits the development of harmful bacterial populations and limits their destructive impact on the intestinal barrier. At the same time, it has a positive

effect on the enrichment of beneficial intestinal flora, strengthens the intestinal defense mechanisms and restores the proper, harmonious symbiotic environment of the intestines.

Clinical recommendations in practice

According to the latest research, specialists should take into account changes occurring in the intestinal microflora in patients with colorectal cancer. According to some, components of the intestinal microflora can be used as new biomarkers for early cancer detection or may be a promising marker for anticancer treatment.[38] In patients with colorectal cancer, specialists should consider sodium butyrate supplementation in combination with ingredients that stimulate butyrate production, such as dietary fiber and omega-3 fatty acids.[39]

Conclusions

Sodium butyrate has a positive effect on the intestinal microflora, reducing inflammation of the mucous membrane and reducing the chances of development and progression of colorectal cancer. Sodium butyrate may prove to be a new, promising form of supporting the treatment of patients with colorectal cancer. Through its molecular actions described in this article, sodium butyrate has anticancer effects. However, the described effect of butyrate requires expanding clinical research and exploring the impact of sodium butyrate directly in people suffering from colorectal cancer. Following a proper diet has a positive effect on the production of butyrate and reduces the risk of developing colorectal cancer. Sodium butyrate may be considered a potential adjunctive therapy in anticancer treatment.

Author's Contribution

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Bibliography

1.Kruh, J. Effects of sodium butyrate, a new pharmacological agent, on cells in culture. Mol Cell Biochem **42**, 65–82 (1981). https://doi.org/10.1007/BF00222695.

2.E.Peter M. Candido, Raymond Reeves, James R. Davie, Sodium butyrate inhibits histone deacetylation in cultured cells, Cell, Volume 14, Issue 1, 1978, Pages 105-113, ISSN 0092-8674, https://doi.org/10.1016/0092-8674(78)90305-7.

3.Davie JR. Inhibition of histone deacetylase activity by butyrate. J Nutr. 2003;133(7 Suppl):2485S-2493S. doi:10.1093/jn/133.7.2485S

4.Moskalev A, Chernyagina E, Kudryavtseva A, Shaposhnikov M. Geroprotectors: A Unified Concept and Screening Approaches. Aging Dis. 2017;8(3):354-363. Published 2017 May 2. doi:10.14336/AD.2016.1022

5. Louis P, Flint HJ. Formation of propionate and butyrate by the human colonic microbiota. Environ Microbiol. 2017;19(1):29-41. doi:10.1111/1462-2920.13589

6. Haraldsdottir S, Einarsdottir HM, Smaradottir A, Gunnlaugsson A, Halfdanarson TR. Krabbamein í ristli og endaþarmi [Colorectal cancer - review]. Laeknabladid. 2014;100(2):75-82. doi:10.17992/lbl.2014.02.531

7. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. Ann Intern Med. 2009;150(1):1-8. doi:10.7326/0003-4819-150-1-200901060-00306

8. Chen S, Wang Y, Zhang L, et al. Exploration of the mechanism of colorectal cancer metastasis using microarray analysis. Oncol Lett. 2017;14(6):6671-6677. doi:10.3892/ol.2017.7044

9.Chen G, Ran X, Li B, et al. Sodium Butyrate Inhibits Inflammation and Maintains Epithelium Barrier Integrity in a TNBS-induced Inflammatory Bowel Disease Mice Model. EBioMedicine. 2018;30:317-325. doi:10.1016/j.ebiom.2018.03.030

10.Hui W, Yu D, Cao Z, Zhao X. Butyrate inhibit collagen-induced arthritis via Treg/IL-10/Th17 axis. Int Immunopharmacol. 2019;68:226-233. doi:10.1016/j.intimp.2019.01.018

11.He Y, Fu L, Li Y, et al. Gut microbial metabolites facilitate anticancer therapy efficacy by modulating cytotoxic CD8+ T cell immunity. Cell Metab. 2021;33(5):988-1000.e7. doi:10.1016/j.cmet.2021.03.002

12. Jaye K, Li CG, Chang D, Bhuyan DJ. The role of key gut microbial metabolites in the development and treatment of cancer. Gut Microbes. 2022;14(1):2038865. doi:10.1080/19490976.2022.2038865

13. Fu X, Liu Z, Zhu C, Mou H, Kong Q. Nondigestible carbohydrates, butyrate, and butyrate-producing bacteria. Crit Rev Food Sci Nutr. 2019;59(sup1):S130-S152. doi:10.1080/10408398.2018.1542587

14. Hanus M, Parada-Venegas D, Landskron G, et al. Immune System, Microbiota, and Microbial Metabolites: The Unresolved Triad in Colorectal Cancer Microenvironment. Front Immunol. 2021;12:612826. Published 2021 Mar 26. doi:10.3389/fimmu.2021.612826

15. Siddiqui MT, Cresci GAM. The Immunomodulatory Functions of Butyrate. J Inflamm Res. 2021;14:6025-6041. Published 2021 Nov 18. doi:10.2147/JIR.S300989

16.Peng L, Li ZR, Green RS, Holzman IR, Lin J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. J Nutr. 2009;139(9):1619-1625. doi:10.3945/jn.109.104638

17.Otani T, Furuse M. Tight Junction Structure and Function Revisited [published correction appears in Trends Cell Biol. 2020 Dec;30(12):1014. doi: 10.1016/j.tcb.2020.10.001]. Trends Cell Biol. 2020;30(10):805-817. doi:10.1016/j.tcb.2020.08.004

18.Zhang Y, Zhang B, Dong L, Chang P. Potential of Omega-3 Polyunsaturated Fatty Acids in Managing Chemotherapy- or Radiotherapy-Related Intestinal Microbial Dysbiosis. Adv Nutr. 2019;10(1):133-147. doi:10.1093/advances/nmy076

19.Kaźmierczak-Siedlecka K, Marano L, Merola E, Roviello F, Połom K. Sodium butyrate in both prevention and supportive treatment of colorectal cancer. Front Cell Infect Microbiol. 2022;12:1023806. Published 2022 Oct 26. doi:10.3389/fcimb.2022.1023806

20.Beam A, Clinger E, Hao L. Effect of Diet and Dietary Components on the Composition of the Gut Microbiota. Nutrients. 2021;13(8):2795. Published 2021 Aug 15. doi:10.3390/nu13082795

21.Gheorghe AS, Negru ȘM, Preda M, et al. Biochemical and Metabolical Pathways Associated with Microbiota-Derived Butyrate in Colorectal Cancer and Omega-3 Fatty Acids Implications: A Narrative Review. Nutrients. 2022;14(6):1152. Published 2022 Mar 9. doi:10.3390/nu14061152

22.Zhuang P, Zhang Y, Shou Q, et al. Eicosapentaenoic and Docosahexaenoic Acids Differentially Alter Gut Microbiome and Reverse High-Fat Diet-Induced Insulin Resistance. Mol Nutr Food Res. 2020;64(10):e1900946. doi:10.1002/mnfr.201900946

23.Zhou E, Rifkin S. Colorectal Cancer and Diet: Risk Versus Prevention, Is Diet an Intervention?. Gastroenterol Clin North Am. 2021;50(1):101-111. doi:10.1016/j.gtc.2020.10.012

24.Merra G, Noce A, Marrone G, et al. Influence of Mediterranean Diet on Human Gut Microbiota. Nutrients. 2020;13(1):7. Published 2020 Dec 22. doi:10.3390/nu13010007

25.Bordonaro M. Further analysis of p300 in mediating effects of Butyrate in Colorectal Cancer Cells. J Cancer. 2020;11(20):5861-5866. Published 2020 Aug 8. doi:10.7150/jca.47160

26.Kang J, Sun M, Chang Y, et al. Butyrate ameliorates colorectal cancer through regulating intestinal microecological disorders. Anti-cancer Drugs. 2023 Feb;34(2):227-237. DOI: 10.1097/cad.0000000000001413. PMID: 36305358; PMCID: PMC9815807.

27.Elimrani I, Dionne S, Saragosti D, et al. Acetylcarnitine potentiates the anticarcinogenic effects of butyrate on SW480 colon cancer cells. Int J Oncol. 2015;47(2):755-763. doi:10.3892/ijo.2015.3029

28.Encarnação JC, Pires AS, Amaral RA, et al. Butyrate, a dietary fiber derivative that improves irinotecan effect in colon cancer cells. J Nutr Biochem. 2018;56:183-192. doi:10.1016/j.jnutbio.2018.02.018

29.Ferreira TM, Leonel AJ, Melo MA, et al. Oral supplementation of butyrate reduces mucositis and intestinal permeability associated with 5-Fluorouracil administration. Lipids. 2012;47(7):669-678. doi:10.1007/s11745-012-3680-3

30. Park M, Kwon J, Shin HJ, et al. Butyrate enhances the efficacy of radiotherapy via FOXO3A in colorectal cancer patient-derived organoids. Int J Oncol. 2020;57(6):1307-1318. doi:10.3892/ijo.2020.5132

31. Kang J, Sun M, Chang Y, et al. Butyrate ameliorates colorectal cancer through regulating intestinal microecological disorders. Anti-cancer Drugs. 2023 Feb;34(2):227-237. DOI: 10.1097/cad.0000000000001413. PMID: 36305358; PMCID: PMC9815807.

32.Ibrahim A, Hugerth LW, Hases L, et al. Colitis-induced colorectal cancer and intestinal epithelial estrogen receptor beta impact gut microbiota diversity. Int J Cancer. 2019;144(12):3086-3098. doi:10.1002/ijc.32037

33.Rejhová A, Opattová A, Čumová A, Slíva D, Vodička P. Natural compounds and combination therapy in colorectal cancer treatment. Eur J Med Chem. 2018;144:582-594. doi:10.1016/j.ejmech.2017.12.039

34.Pardede SO, Paramastri KA, Hegar B, Rafli A. The Proportion of Bifidobacterium and Escherichia coli in Colon of Children with Recurrent Urinary Tract Infection. Saudi J Kidney Dis Transpl. 2020;31(5):898-904. doi:10.4103/1319-2442.301196

35.Chen G, Ran X, Li B, et al. Sodium Butyrate Inhibits Inflammation and Maintains Epithelium Barrier Integrity in a TNBS-induced Inflammatory Bowel Disease Mice Model. EBioMedicine. 2018;30:317-325. doi:10.1016/j.ebiom.2018.03.030

36.Pardede SO, Paramastri KA, Hegar B, Rafli A. The Proportion of Bifidobacterium and Escherichia coli in Colon of Children with Recurrent Urinary Tract Infection. Saudi J Kidney Dis Transpl. 2020;31(5):898-904. doi:10.4103/1319-2442.301196

37.Kang J, Sun M, Chang Y, et al. Butyrate ameliorates colorectal cancer through regulating intestinal microecological disorders. Anti-cancer Drugs. 2023 Feb;34(2):227-237. DOI: 10.1097/cad.0000000000001413. PMID: 36305358; PMCID: PMC9815807.

38. Tsiaoussis J, Souglakos J. Microbiota: An Emerging Biomarker in Colorectal Cancer. Cancers (Basel). 2021;13(21):5530. Published 2021 Nov 4. doi:10.3390/cancers13215530

39.Han S, Van Treuren W, Fischer CR, et al. A metabolomics pipeline for the mechanistic interrogation of the gut microbiome. Nature. 2021;595(7867):415-420. doi:10.1038/s41586-021-03707-9