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The Emerging Role of Short Chain Fatty Acids in Human Physiology

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Abstract: *The gut microbiota produces short chain fatty acids by fermenting partially digested polysaccharides. These are important molecules. SCFAs are most concentrated in the proximal colon, where they are either absorbed into the bloodstream or used locally by enterocytes. SCFAs inhibit histone deacetylases (HDACs) and activate G-protein-coupled receptors (GPCRs), inclusive of GPR43, GPR41, and GPR109A. A variety of biological effects result from the inhibition of HDACs, which alters gene expression. While the complete extent of SCFA mediated HDAC suppression has to be investigated, GPCRs' role in controlling immunological responses, inflammation, and metabolism is well recognized.Numerous biological functions, including as phagocytosis, chemotaxis, reactive oxygen species (ROS) generation, cell division, and function, are impacted by SCFAs. They also help to preserve the integrity of the gut and have antibacterial, antitumorigenic, and anti-inflammatory qualities. Given that SCFA levels are largely diet-dependent, their effects help explain the rising prevalence of inflammatory diseases in Westernized societies, where dietary patterns are often low in fiber and high in processed foods.*

Keywords: Histone deacetylases, fiber, heptahelical receptors , microbiota, and short chain fatty acids

I. INTRODUCTION

- These fatty.acids have a structure/with lower than six carbon atoms, which are not found in nature as testifier triglycerides.
- This kind of fatty acids are produced to a greater extent in the caecum and proximal colon by microbial fermentation of oligo and polysaccharides[1].

SCFAs are created by the microbial in the large intestine,as a consequence of anaerobic fermentation of indigestible polysaccharides. These tiny organic monocarboxylic acids, which include resistant starch and dietary fiber, have chains as long as six atoms.It is composed mostly of Acetate, propionate, and butyrate make up the majority of its composition, with a about 60:20:20 molar ratio for each [2].

Numerous commensal bacteria can be found in the human body.

The epidermis and several mucosal cavities, including the nasal., oral, pulmonary, and vaginal, are colonised by the host microbiota. They do, however, grow to remarkable densities in the gastrointestinal (GI) tract. For possible mutual advantage, trillions of bacteria, fungi, and viruses live in symbiosis with the host [3].

SOURCE AND FUNCTIONS:

Butyrate;, propionate, and acetate are the three SCFAs that are most prevalent in the intestineSCFAs influence a wide range of cell types to control vital biological functions, such as immunity, intestinal function, and host metabolism [4].

Acetate

Anaerobic bacteria in the animal colon break down food fibers, which produce the majority of acetate. Numerous bacterial species, including A. muciniphila and Bacteroides spp., generate acetic acid by fermentation. The conversion of this process to acetate is mostly mediated by glycolysis-produced acetyl-CoA; butyryl-CoA:acetyl-CoAtransferase

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enzymatically converts it to butyrate. Acetate exists in the circulation as a free acid and is mostly processed in the muscles, heart, brain, and liver [5][6].

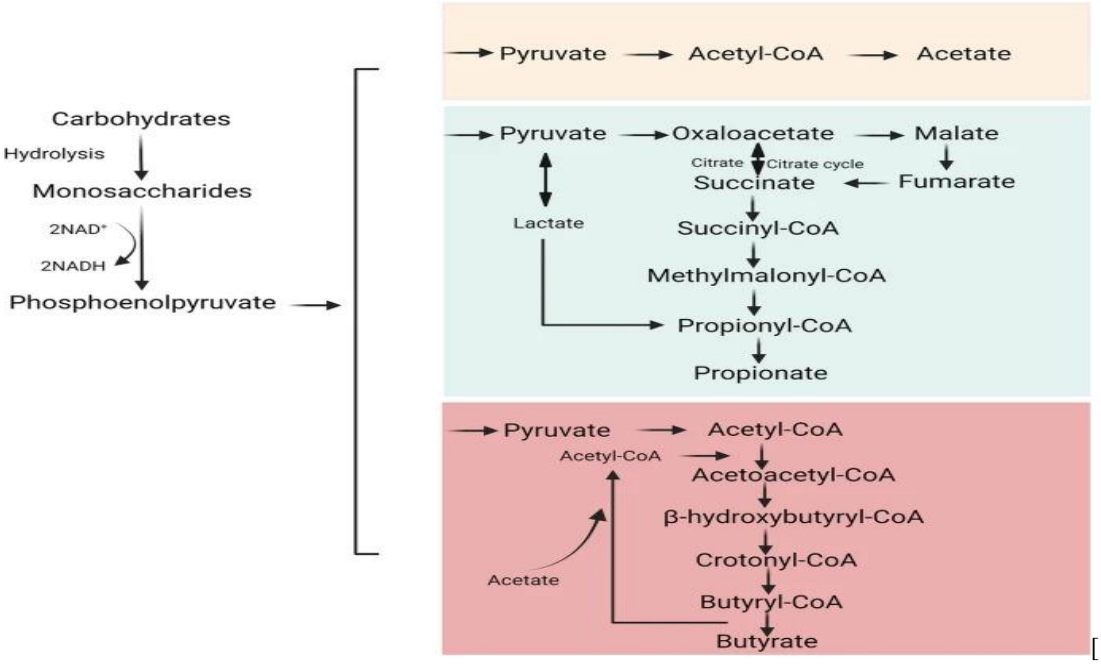
Propionate

The methylmalonyl-CoA decarboxylase (mmdA) gene is widely found in Bactericides and several Negativeness, indicating that propionate is mostly formed from carbohydrate metabolism during glycolysis, specifically via the succinate route (fig. 1). Gram negative bacteria such as Roseburia inulinivorans and Muciniphila , Bactericides [8][9].

Butyrate

Human host IECs absorb butyrate, which is produced by a range of commensal bacteria, including as Clusters IV and XIVa of Clostridium, and Prausnitzii. Butyrate is necessary for colon cells to maintain their energy supply.Glycolysis transforms carbohydrates to butyrate by joining two acetyl-CoA molecules to form acetoacetyl-CoA, which is then reduced stepwise to butyryl-CoA [7].

[Fig-1]:



[10]

AVAILABILITY OF SCFA's:

- SCFA generation occurs in-vivo through dietary fiber fermentation.
- SCFAs are produced naturally through metabolic activities.
- SCFA's intake via food.
- Pharmacokinetics of SCFA's.
- SCFA's in health and disease.

Using SCFAs as a treatment for inflammatory illness. [11]

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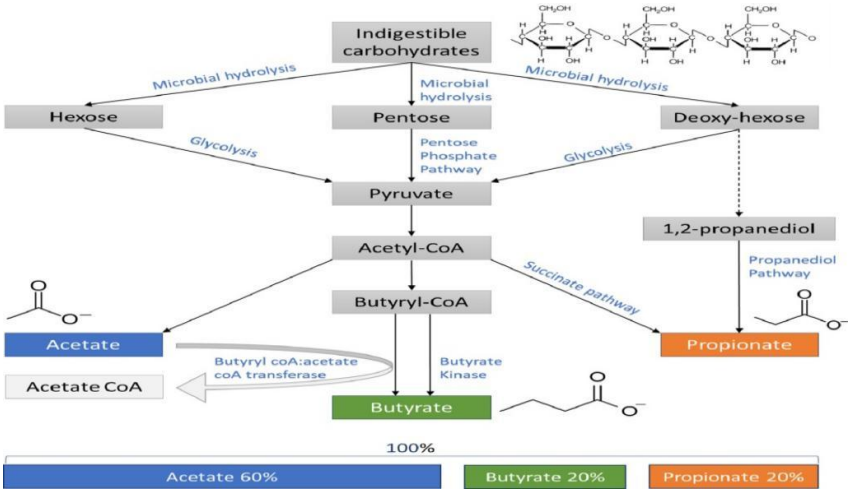


(fig-2)[12]

ROLE OF SCFA's IN THE BODY:

Digestive health

Inflammation:

Inflammatory skin diseases, including urticaria, psoriasis, acne, and atopic dermatitis (AD), can cause significant burden and comorbidities [13].

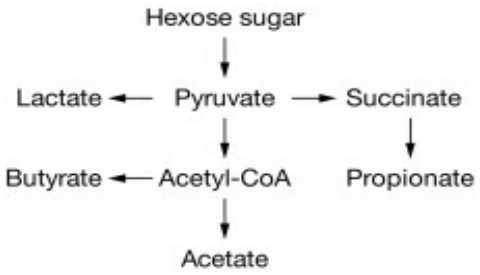
Gut brain axis:

SCFAs. play a confined role in mediating the influence of microbial-targeted therapy on cognitive and affective functioning, especially in humans.It is explained how SCFAs affect cellular systems and how they interact with immunological, endocrine, neurological, and humoral gut-brain signaling pathways [14].

Metabolism:

The three primary short-chain fatty acid groups are butyric, propionic, and acetic. They are very soluble and are absorbed easily from the gut lumen into the bloodstream(fig-3). Short-chain fatty acids are used as substrates for the production of ketone molecules and longer-chain fatty acids.They can also be oxidized to produce energy, which is believed to be crucial for stomach lining cells.[15].

(fig-3)



Weight management:

A substantial amount of animal research suggests that acetate may have a major regulatory role in insulin sensitivity and body weight regulation via affecting glucose homeostasis and lipid metabolism. [17].

Energy homeostasis

Immune regulation:

By stimulating PTX-sensitive GPCRs in immune cells, including human monocytes, SCFAs help to inhibit the inflammatory response by promoting the release of prostaglandin E2 and the synthesis of the cytokine IL-10 [17].

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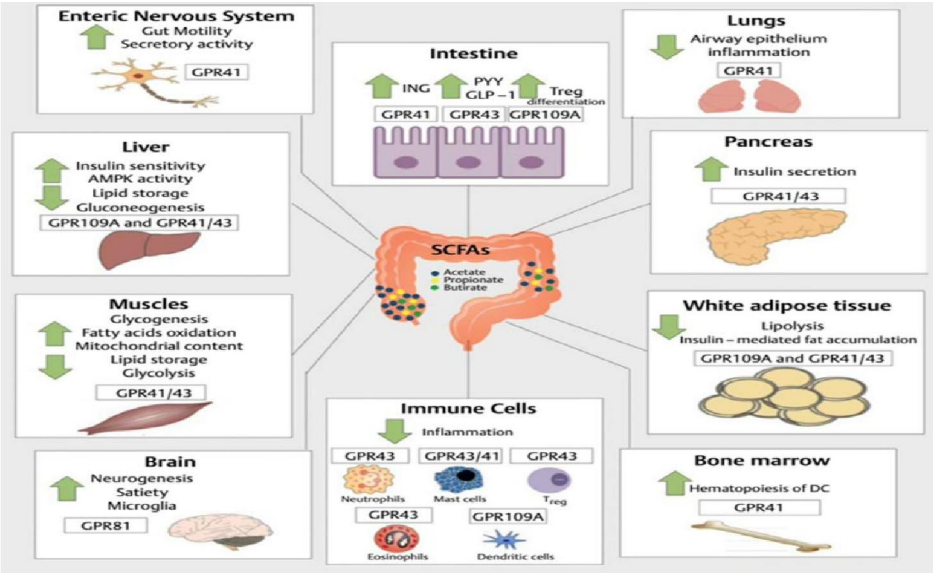
Brain health

Mineral absorption:

Fibers have the ability to bind minerals together in the small intestine.When the fiber ferments in colon, the bound minerals are released and subsequently absorbed when short chain fatty acids , a fermentation product, are present.

It has been proposed that butyric (Bu), propionic (Pr), and acetic (Ac) acids improve the rat colon's absorption of calcium and magnesium [18].

(fig-4)



[19]

PHARMACOLOGICALACTIONS:

SCFA's mediated regulation of mucosal immunity:

SCFAs have the ability to directly control immune cell activation, differentiation, tissue tropism, and the acquisition of tolerogenic/inflammatory behavior. Tregs, Th17 cells, and T helper cell 1 (Th1) differentiation are all impacted by SCFAs.This suppresses and enhances Treg differentiation and Foxp3 expression.Similarly, SCFAs increase the expression of interleukin-10 by macrophages and lymphocytes (T and B cells) by blocking HDAC [20][21].

Neurological disorders including imbalanced SCFA levels:

By preserving the integrity of the blood-brain barrier, preventing neuro-inflammation, promoting serotonin production, SCFAs that enter the bloodstream may help maintain CNS homeostasis. Low levels of SCFAs have been connected to several neurological disorders since they are necessary for preserving CNS homeostasis. These alterations are linked to the infiltration of peripheral immune cells into the central nervous system (CNS), which promotes neurodegeneration and neuroinflammation. [22] [23].

Ulcerative colitis:

The colon and rectum are the primary sites of the pathogenic changes, which are often limited to the mucosal layer.The concentrations of SCFA acetate and propionate in research participants were lower than healthy people. According to the current research, UC patients have significantly lower levels of acetate, propionate, valerate, total SCFAs than do healthy people. This showed that the colon's butyrate supply was compromised, which could lead to colonocytes not having enough energy [24][25].

Radiation proctitis:

Treatment for chronic radiation proctitis is currently limited.However, there is no evidence that butyric acid enemas are better than a placebo. [5]. Butyric acid enemas don't seem to work any better than a placebo for treating chronic radiation proctitis [26][27].

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Antibiotic associated diarrhoea:

Severe cases and small disturbances are both possible with pseudomembranous colitis. Diarrhea and total SCFA levels did not link, however there were significant disruptions in the gut microbiota and SCFA concentrations dropped. After undergoing a fecal enema, most patients with severe diarrhea recovered clinically in 4 days [28].

Autoimmune diseases:

Celiac diseases:

Mostly demonstrates elevated levels of total SCFAs, which are also observed in individuals with celiac disease on treatment [7]. CD is an autoimmune illness that is immune-mediated.Gliadin peptide fragments, a peptide found in gluten, are presented to the adaptive immune system by APCs through human leukocyte antigens (HLA) proteins, leading to tissue transglutaminase auto-antibodies being produced, which causes autoimmune-like symptoms [29][30].

Asthma:

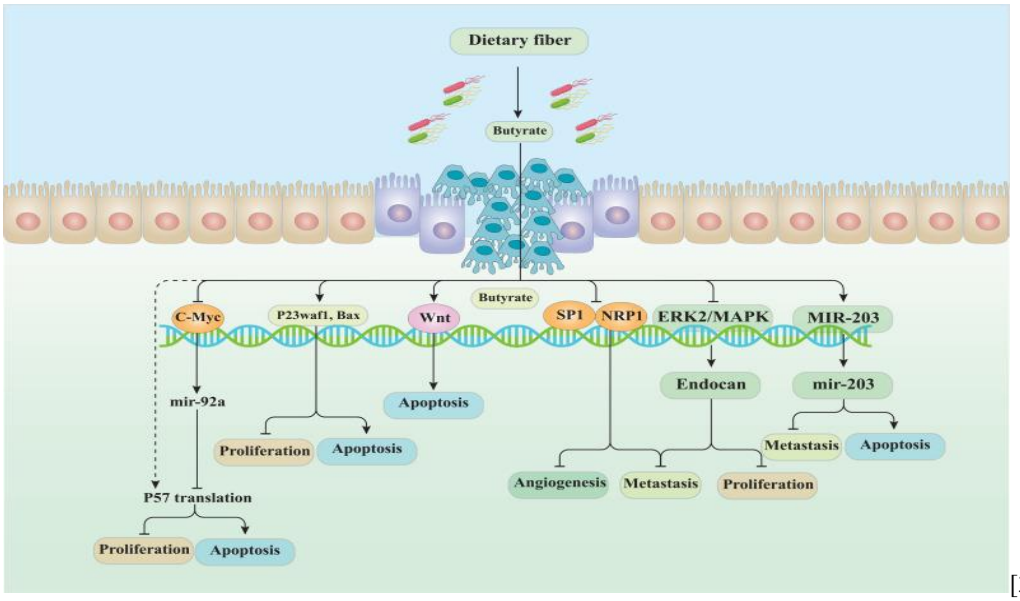
Eosinophil and total inflammatory cell counts have significantly decreased. SCFAs have a down-regulating effect on the inflammatory pathway and allergic immunological response in asthma.The group that was given sodium propionate showed noticeably less airway hyperresponsiveness.. The treatment of SCFA also significantly reduced the expression of IL-1 beta, an inflammasome cytokine, and the OVA-specific IgE level [31].

Cancer therapy:

Bladder cancer:

The formation of bladder cancer cells is directly inhibited by SCFAs, which also cause programmed cell death (fig. 5). Patients with bladder cancer who have lower butyrate levels may have less IEC growth and proliferation, which would lessen the malignancy's detrimental effects.Consumption of fruit has a positive correlation with both butyrate and Prevotella counts.[31] [32].

(fig-5)



[34]

II. CONCLUSION

In biological studies, the gut microbiota has received a lot of interest lately, with mounting evidence suggesting that abnormalities in intestinal bacterial populations could be a contributing factor to the onset of various health disorders. One significant component of the intricate and multi-mechanism correspondence between the microbiota and its host is the biochemical signals produced by the bacteria. Short-chain fatty acids., produced by gut bacteria, have been shown to influence not just immunity, metabolism, and gastrointestinal function, but also the growth and upkeep of the central nervous system (CNS).Although significant strides have been made in understanding microbiota-host interactions,

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much remains to be discovered, particularly in the realm of microbiota-gut-brain communication. Since most of the research to date has been conducted on animal models—rats in particular—extra caution is needed when extrapolating these findings to humans. SCFAs have been shown to impact CNS functions in both direct and indirect ways, affecting behavior, mood, and cognitive performance. Understanding how these metabolites impact gut-brain transmission could lead to new therapeutic approaches for central nervous system disorders.In addition, SCFAs may provide a promising dietary therapy to enhance many psychological processes due to their possible role in promoting brain health.

AUTHOR CONTRIBUTIONS

Performed experiment/data collection[4]
Data analysis and interpretation[2]
Provided funding[3]
Primary author[1]

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