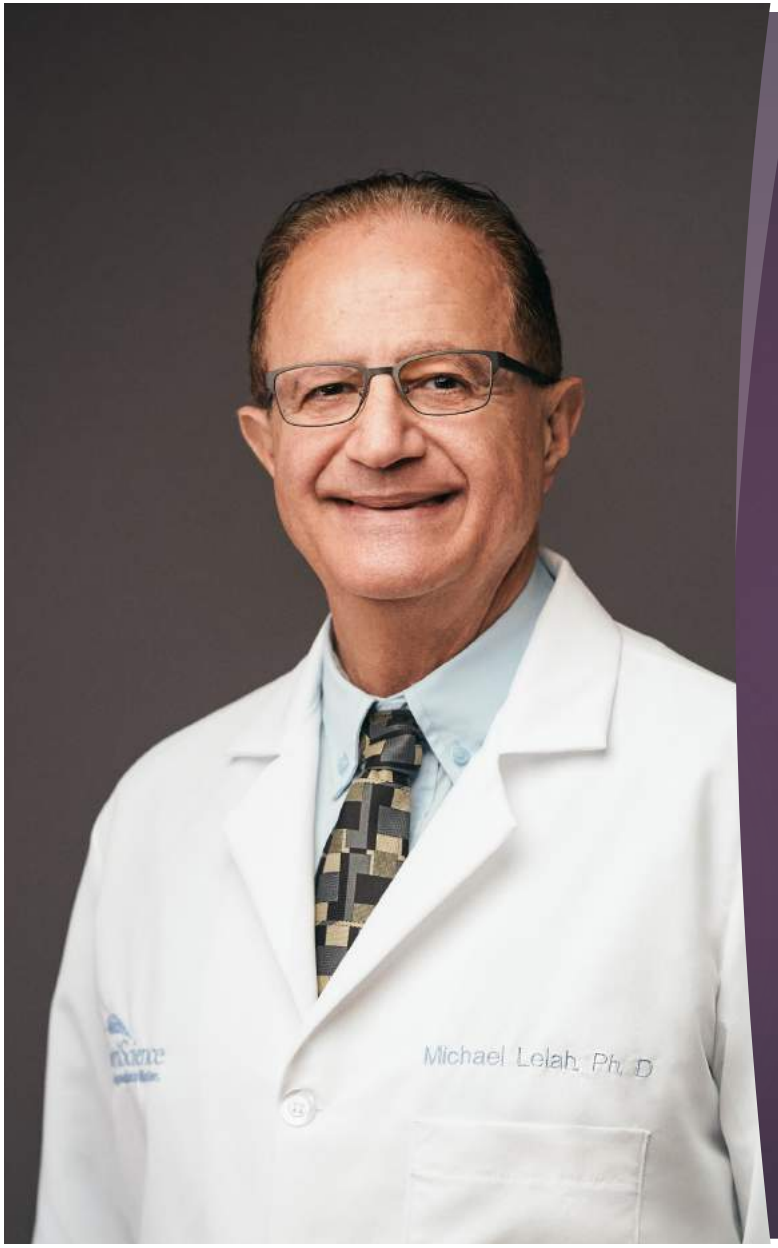

Next Generation Prebiotics: Direct Butyrate Generators

Michael Lelah, Ph.D. Chief Science Officer

NutriScience Innovations

Naturally Informed's Microbiome:

Mastering The Market

May 17, 2022

Overview

- What is Butyrate?
- Why Butyrate?

- How is Butyrate generated in the body?
- What is the role of Butyrate in health?
- How does Butyrate work? - Mechanisms of action

- What is a direct butyrate generator?
- Types of butyrate generators
- Is a direct butyrate a prebiotic, postbiotic, or what?

- What's next?

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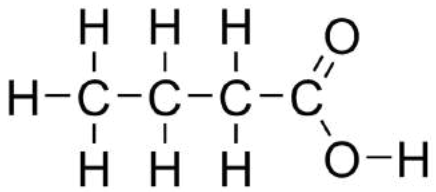
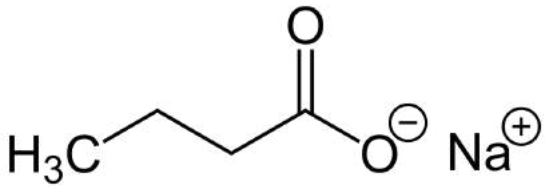
What is Butyrate?

Butyrate is a Short Chain (C4) Fatty Acid (SCFA) – an organic acid





Other Short Chain Fatty Acids (SCFA)

- Acetate (C2)
- Propionate (C3)
- Valerate (C5)

Butyrate is the least abundant SCFA in humans:

- 60% acetate
- 25% propionate
- 15% butyrate

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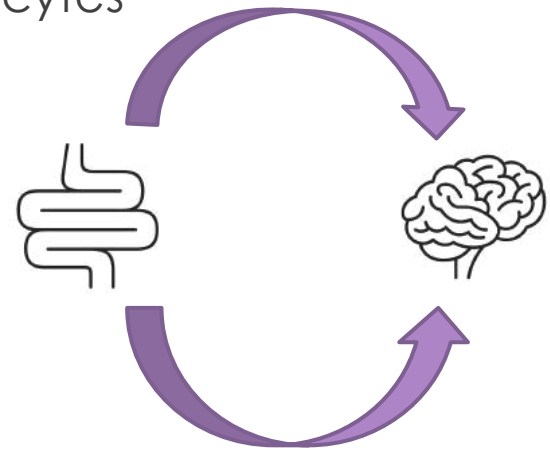
Why Butyrate?

- Butyrate is the **major energy source** for colonocytes
  - Butyrate accounts for ~70% of ATP produced by colonocytes
- Butyrate is a **signaling molecule**
  - 2 main mechanisms of action



- Butyrate's effects on health are:
  - At the **intestinal level** - colonic/gut health
  - At the **extraintestinal level** – effects on organ health and diseases

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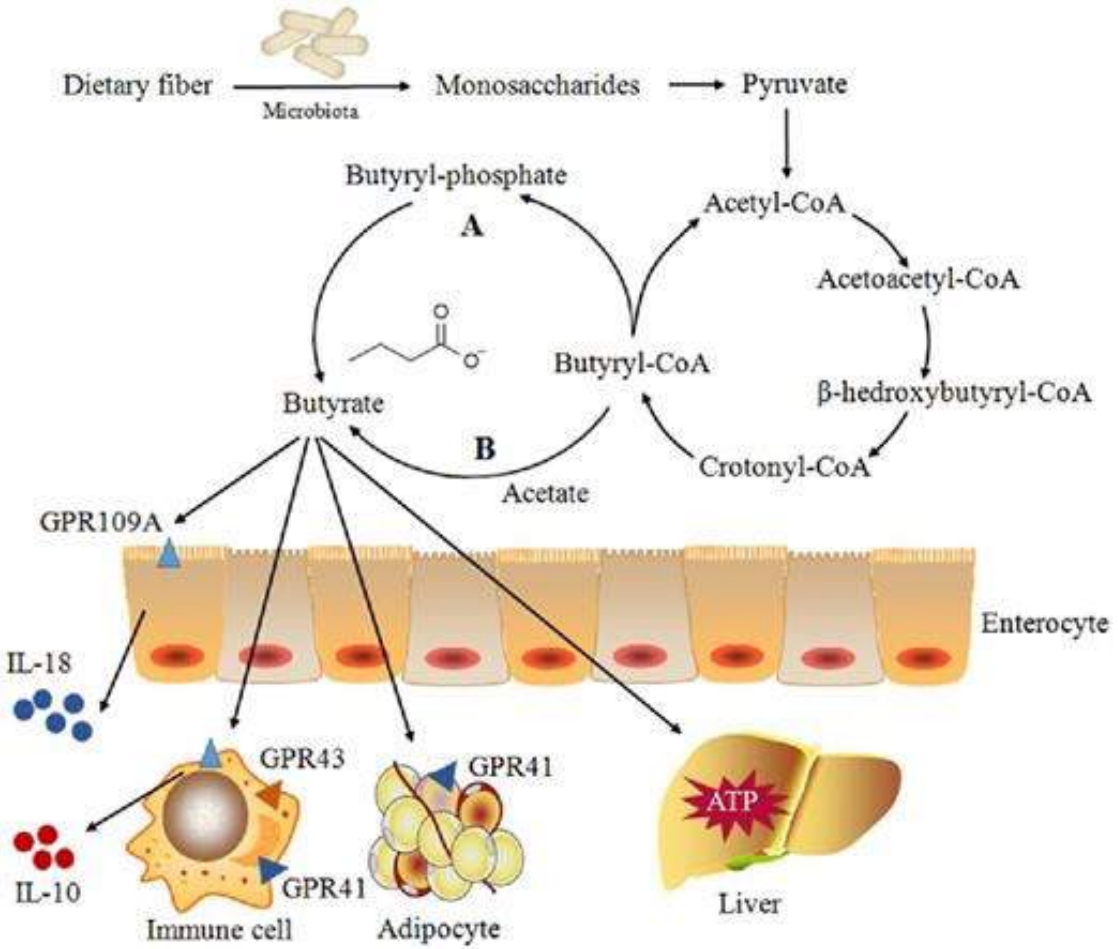
How is Butyrate Generated in the Body?

- Butyrate is produced in the intestinal lumen by **bacterial fermentation** of mainly undigested dietary carbohydrates
- Most micro-organisms ferment carbohydrates, so the concentration of Butyrate is **highest in the proximal colon**, where most substrates for fermentation are available, and declines towards the distal colon
- The ability to produce butyrate is widely distributed among the **Gram-positive anaerobic** bacteria that inhabit the human colon.



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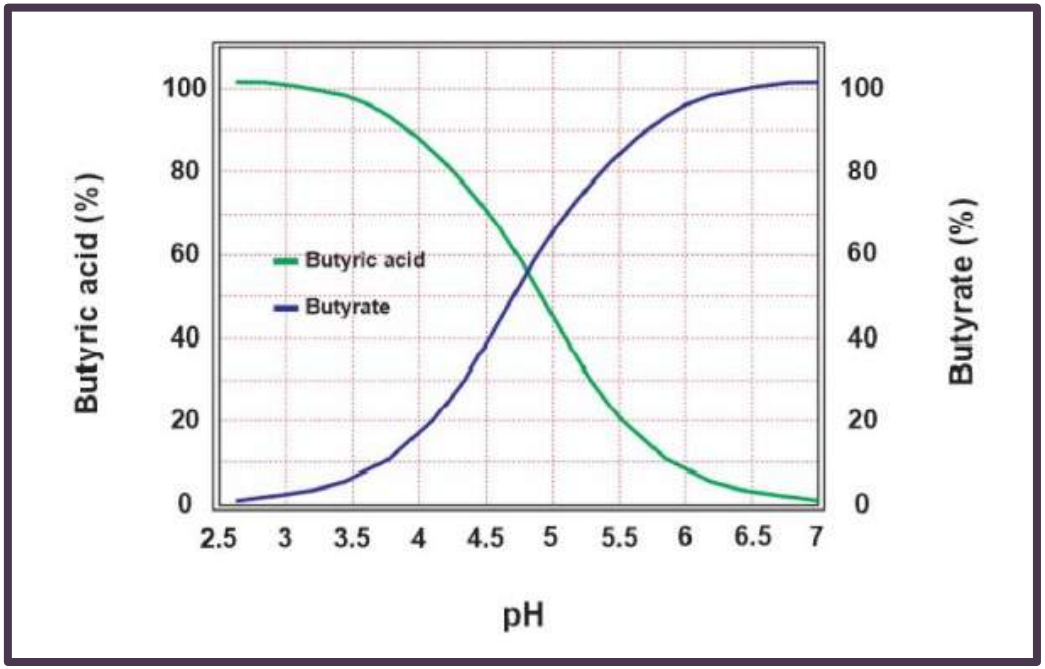
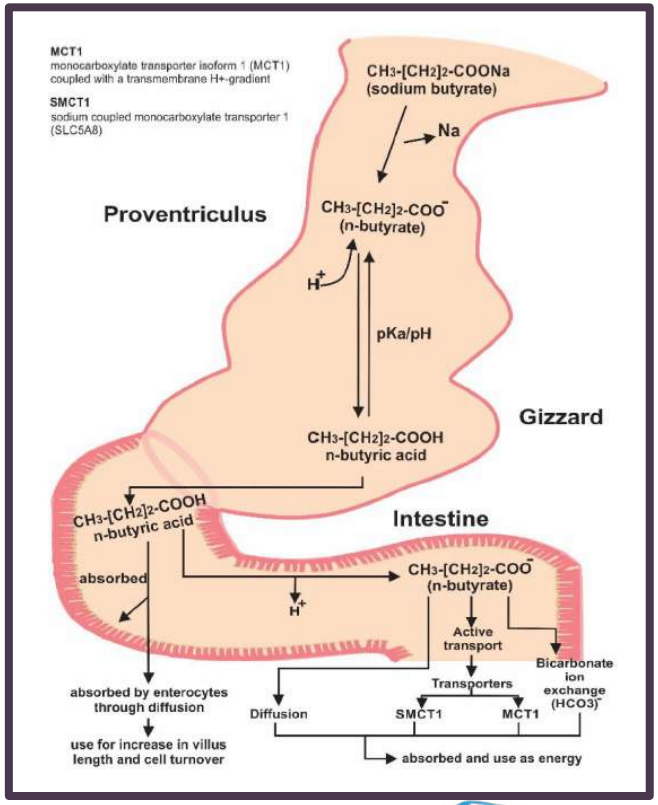
What Form does Butyrate Exist in the Body?

- It depends on the lumen pH





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Butyrate and Health – Intestinal Effects

- Intestinal level – **gut health**
- Barrier integrity – "leaky gut"
- Healthy microbiome – lower pH
- Energy regulation
- Ion absorption and transportation – Na^+ and Cl^-
- Cell growth and differentiation – anti-carcinogenesis
- Anti-inflammatory - nuclear factor κB (NF-κB) activation
- Antioxidant – oxidative stress reduction

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Butyrate and Health – Extraintestinal Effects 1

- **Gut-brain axis**
  - Ability to cross the blood-brain barrier
  - Mood and sleep
  - Appetite and eating behavior
- **Immune function**
  - Intestinal barrier
  - Immune cell activation
  - Anti-microbial peptide (AMP) signaling

- **Metabolic syndrome / Obesity**
  - Increased insulin sensitivity
  - Increased glucose tolerance
  - Glucagon-like peptide (GLP-1) secretion
- **Anti-aging effects**
  - Histone deacetylase (HDAC) inhibitor
  - Neuro-inflammation inhibition
  - Oxidative stress reduction
- **Synergism with Vitamin D**
  - Upregulation of Vit D receptor

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Butyrate and Health – Extraintestinal Effects 2

- **Gut-Skin Axis**
  - Regulation of psoriasis, atopic dermatitis, acne
- **Gut-Liver Axis**
  - Alcohol liver disease (ALD)
  - Non-alcoholic fatty liver diseases (NAFLD)
  - Lipid biosynthesis and metabolism
- **Gut-Heart Axis**
  - Cardiovascular protective effects
  - Atherosclerosis, myocardial ischemia

- **Gut-Lung Axis**
  - Allergic asthma
- **Gut-Kidney Axis**
  - Kidney function
- **Gut-Thyroid Axis**
  - Thyroid health
- **Gut-Eye Axis**
  - Butyrate receptors in the eye
- **Long Covid symptoms**
  - Butyrate producing bacteria

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Mechanisms of Action

Butyrate has 2 Primary Mechanisms of Action

Histone Deacetylase (HDAC) Inhibition

- Enzymes regulate gene expression and protein activity
- Butyrate inhibits activation of HDAC
- Most cells have HDAC activity

Free Fatty Acid Receptor (FFAR) activity

- Butyrate binds to FFAR2 and FFAR3 receptors
- Many cells (gut, nerve, epithelial, immune, etc) have these receptors
- Newly discovered class of G-protein coupled receptors (GPCR)
- Most signaling cascades occur through this receptor

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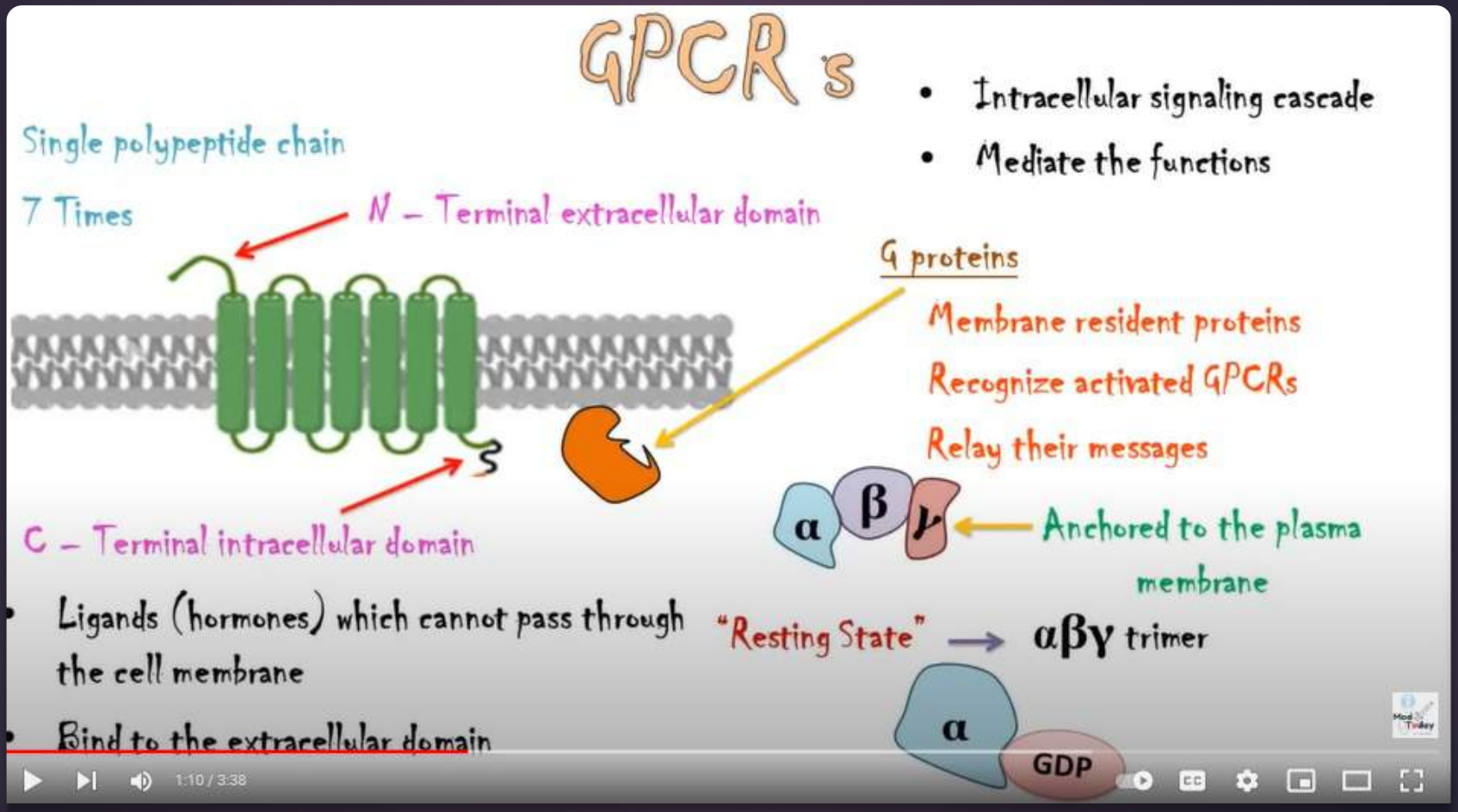
G-Protein Coupled Receptors (GPCR)



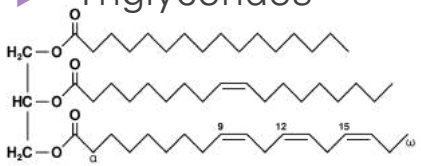
Direct Butyrate Generation

- Butyrate generation by the gut microbiome/probiotics
  - **Indirect generation**
    - prebiotic -> microbiome bacteria probiotics -> butyrate (postbiotic)
- **Sodium Butyrate**
  - Directly feed butyrate – not practical
- **Direct Butyrate generation**
  - Generation of Butyrate directly in the intestines
  - Next generation prebiotics

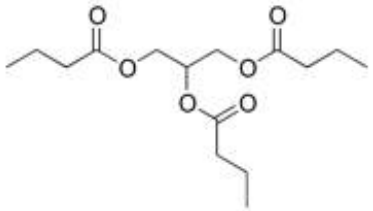
Direct Butyrate Generators -1

Foods / Dietary Supplements

- Tributyrin
  - Triglycerides



  - Glycerol tributyrate



- Found naturally in butterfat
- Used in making margarine
- "Oleomargarine" French Chemist - Hippolyte Mege-Mouries 1860's
- Cheesy flavor, acrid taste
- Hydrolyzed by esterases in the intestines to Butyrate
- Typical human dose 300 mg/day
- Suitable for human and animal (farm/companion animals)

Tributyrin pK Studies (rat)

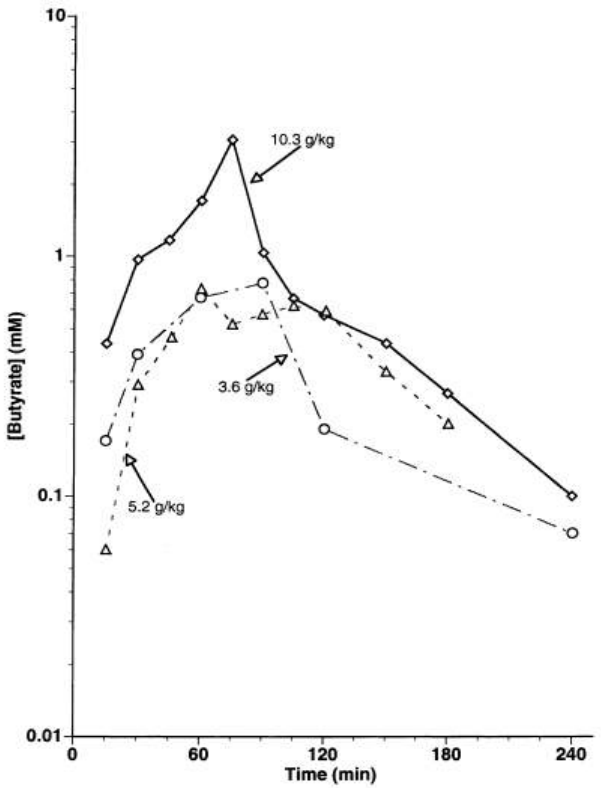


Fig. 4 Concentrations of butyrate determined in the plasma of rats given enteral tributyrin at doses of 10.3 (◇——◇), 5.2 (△- - -△), or 3.6 (○-·- -·-○) g/kg. *Symbols* represent mean values recorded for 3–5 rats studied at each dose

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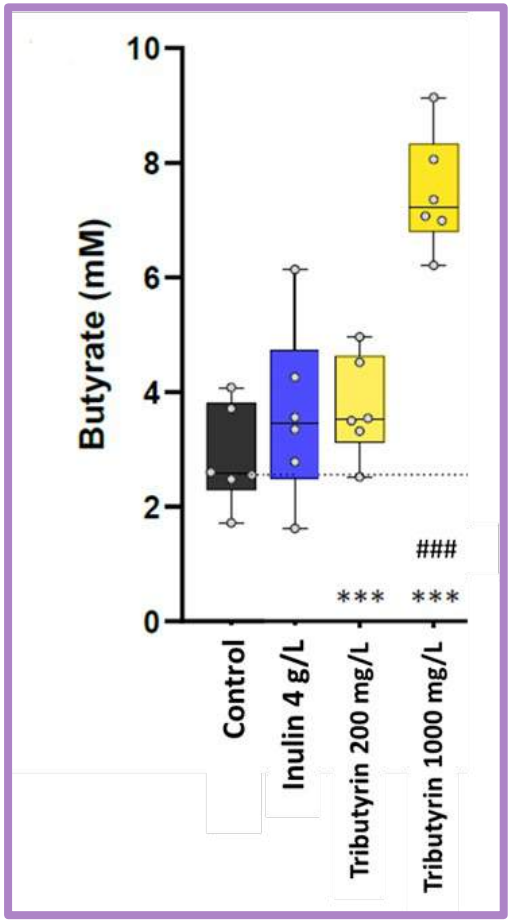
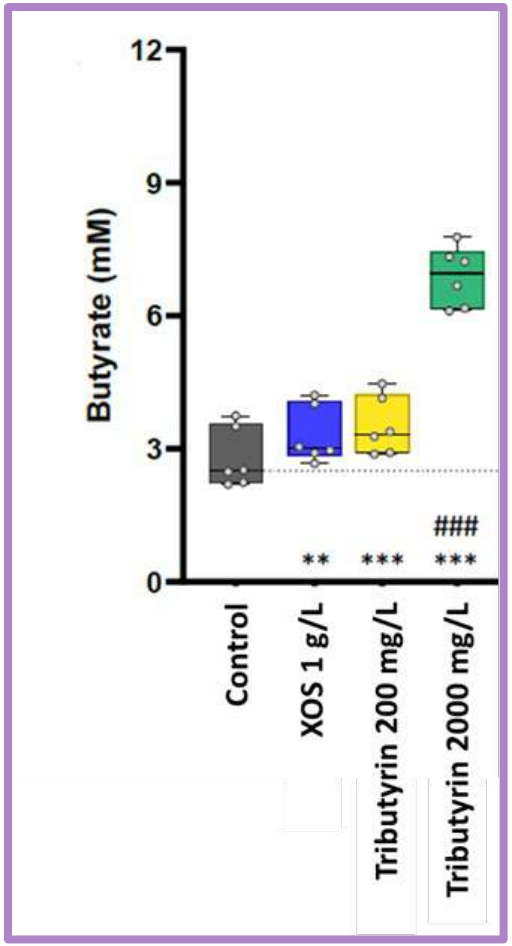
Butyrate Generation from Tributyrin





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Direct Butyrate Generators -2

Foods / Dietary Supplements

- Butyrate Salts
  - Calcium, Magnesium salts
  - Reduced unpleasant taste and odor
  - Less volatile
  - Hygroscopic and deliquescent
  - Poor water solubility

- Beta-HydroxyButyrate (BHB) and salts
  - Ketone generation
  - BHB is converted into acetyl-CoA
  - But is it converted to butyrate?

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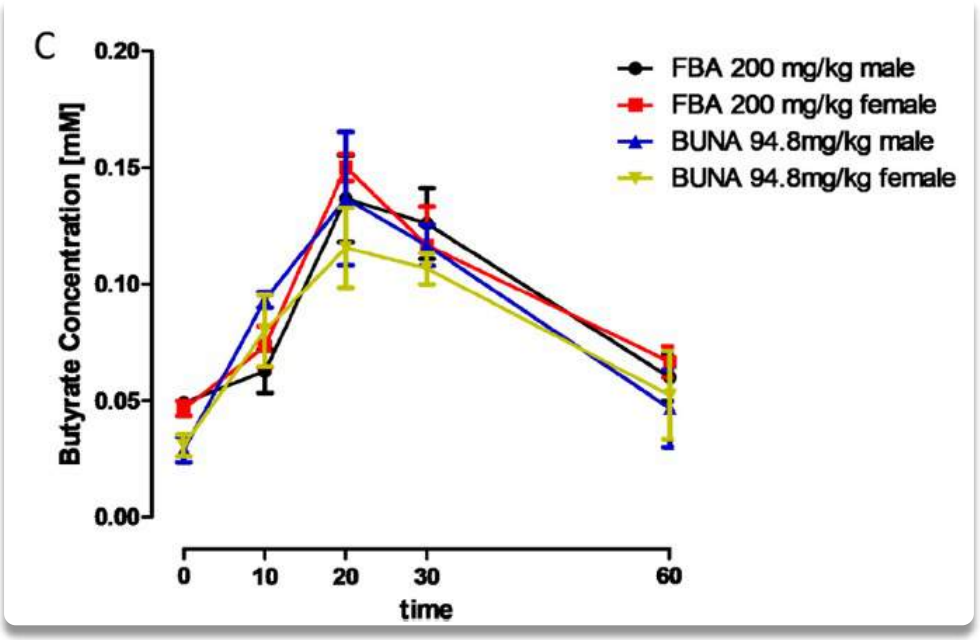
Direct Butyrate Generators - 3

Drugs (Pro-drugs)

- N-(1-carbamoyl-2-phenyl-ethyl) butyramide aka Phenylalanine-Butyramide (FBA)
  - Patented Butyrate generator
- Pivaloyloxymethyl butyrate
  - Anticancer activity
- Cholesteryl butyrate
- Butyryl-L-carnitine



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Are Direct Butyrate Generators Prebiotics or Postbiotics?

Prebiotic - prebiotics are products or ingredients that are utilized in the microbiota producing a health or performance benefit

Postbiotics - postbiotics are functional bioactive compounds, generated in a matrix during fermentation, which may be used to promote health

Are Direct Butyrate Generators Prebiotics or Postbiotics?

- Butyrate is clearly a **postbiotic**
- Is a direct butyrate generator such as Tributyrin, a prebiotic, postbiotic or something else?
- Technically, Direct Butyrate Generators are a Pro-drug - a biologically inactive compound that can be metabolized in the body to produce a drug – but this term is not suitable for foods/supplement use or communication with consumers
- Direct Butyrate Generators may be classified as **prebiotics** – they generate postbiotics, although not via bacteria
- Direct Butyrate Generators may also be called **postbiotics** – this is more marketing / consumer-friendly

Brand and Consumer Awareness of Butyrate

- **Brand** awareness – gaining interest/growing
  - Less than a dozen butyrate products (supplements) currently on the market
- **Consumer** awareness – very early/limited

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The Next Generation

- Direct generation of butyrate
- Independent of the State of the Microbiome
- Scientific research – very early
- Products – expect to see more activity over the next few years
- Brand awareness – growing
- Consumer awareness – limited

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THANK YOU !

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