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The microbiome and its pharmacological targets: therapeutic avenues in cardiometabolic diseases

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Consisting of trillions of non-pathogenic bacteria living in a symbiotic relationship with their mammalian host, the gut microbiota has emerged in the past decades as one of the key drivers for cardiometabolic diseases (CMD). By degrading dietary substrates, the gut microbiota produces several metabolites that bind human pharmacological targets, impact subsequent signalling networks and *in fine* modulate host's metabolism. In this review, we revisit the pharmacological relevance of four classes of gut microbial metabolites in CMD: short-chain fatty acids (SCFA), bile acids, methylamines and indoles. Unravelling the signalling mechanisms of the microbial–mammalian metabolic axis adds one more layer of complexity to the physiopathology of CMD and opens new avenues for the development of microbiota-based pharmacological therapies.

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Chemical compounds studied in this article
Acetate (PubChem CID: 176) Butyrate (PubChem CID: 264) Cholic acid (PubChem CID: 221493) Chenodeoxycholic acid (PubChem CID: 10133) Deoxycholic acid (PubChem CID: 222528) Indole-3-propionate (PubChem CID: 3744) 3-indoxylsulfate (PubChem CID: 10258) Propionate (PubChem CID: 1032) Trimethylamine (PubChem CID: 1146) Trimethylamine-*N*-oxide (PubChem CID: 1145)

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Introduction

Cardiometabolic diseases (CMD) present a complex array of interrelated risk factors affecting more than one billion people with a dramatic impact on mortality, morbidity and quality of life [1]. These factors (including impaired glucose tolerance, dyslipidemia, arterial hypertension, insulin resistance and central obesity) are epidemiologically clustered — the presence of at least three of five of these symptoms corresponding to the 'metabolic syndrome' clinical diagnosis [1]. Although many pharmacological mechanisms have been suggested, the underlying causes of CMD and its potential therapeutic avenues remain to be fully explored. With the advent of high-throughput methodologies (metagenomics, metabolomics), the gut microbiome emerged as one of the key drivers for CMD [2]. The gut ecosystem, as well as its individual members, was shown to contribute to the host metabolism [3•]. A lower bacterial gene count (LGC) is associated to increased adiposity, insulin resistance and dyslipidemia [4••] and dietary intervention can improve both bacterial gene richness and clinical metabolic outcomes [5••]. Patients with type 2 diabetes (T2D) also show specific compositional and functional changes in their metagenomes [6••].

With the increasing number of clinical studies reporting associations between the composition of the gut microbiota and CMD outcomes, one question arises — how are these changes in microbial ecology translated into pharmacological messages to the mammalian host? Consisting of trillions of non-pathogenic bacteria living in a symbiotic relationship with their host, gut microbiota produces several signalling molecules (e.g., LPS, peptidoglycans, but also metabolites) that bind host proteins and impact signalling networks, therefore playing a central role as chemical messengers in the microbial–mammalian crosstalk [7]. The identification of the pharmacological targets and signalling pathways of these metabolites is key to a better understanding the molecular crosstalk supporting the microbial–mammalian metabolic axis — and provides a suitable framework for the discovery of the mechanistic basis of these associations. In this context, fine mapping of the microbial signalling metabolome and its host molecular targets opens up novel pharmacological avenues for microbiome interventions.

The microbiome interacts with its host through microbial metabolites

In this review, we shall present four classes of gut microbial metabolites impacting host molecular mechanisms

relevant to CMD: short-chain fatty acids (SCFA), bile acids, methylamines and indoles.

SCFA

Fermentation of otherwise indigestible dietary fibre by gut bacteria produces mostly SCFA (e.g., formate, acetate, propionate, butyrate, isobutyrate, valerate, isovalerate), which can act either as substrates and/or signalling molecules [8] (Figure 1).

Butyrate is the primary substrate and energy source used by colonocytes [9]. Once inside the cell, butyrate is converted to acetyl-CoA by β-oxidation and enters the tricarboxylic acid cycle (TCA cycle) for energy production [8], which leads to an inhibition of autophagy [10].

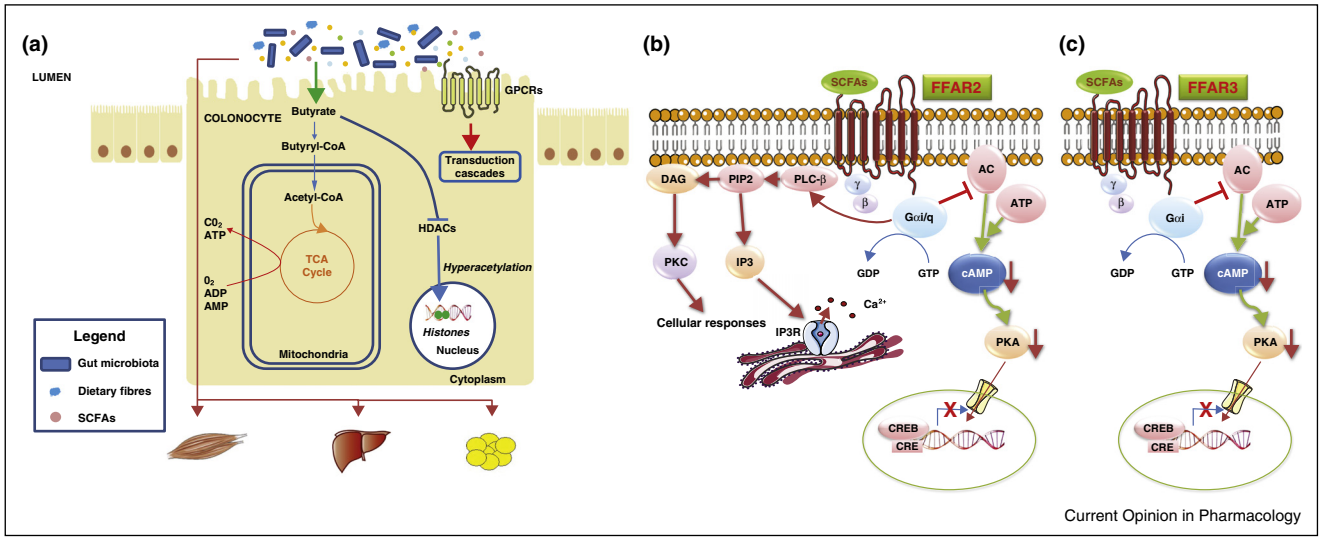
While propionate is largely metabolised in the liver, acetate is the main SCFA in plasma [11]. After crossing the blood brain barrier, acetate has shown to suppress appetite and induce hypothalamic neuronal activation, thus modifying acetyl-CoA carboxylase activation and expression of neuropeptides responsible for appetite suppression [12•]. SCFA also trigger the production of glucagon-like peptide-1 (GLP-1), a gut hormone with anorexigenic properties [13•,14,15].

SCFAs also act as ligands for G protein-coupled receptors, therefore activating subsequent signalling pathways: activation of FFAR2 and FFAR3 by SCFA results in the inhibition of cAMP production via interaction with Gαi or Gαi/q, respectively [16].

FFAR2 activation by SCFAs seems to have a role as a sensor for excessive dietary energy, as its activation suppresses insulin sensitivity and fat accumulation in adipose tissue and increases insulin sensitivity in liver and muscle, thus regulating energy balance [17•]. Moreover, FFAR2 activation is also able to modulate immune responses [18]. Conversely, FFAR3 activation increases leptin secretion, a hormone that acts as a signal of satiety [19]. Butyrate and propionate promote intestinal gluconeogenesis — which has beneficial effects in glucose homeostasis — by complementary mechanisms: the first by activating intestinal gluconeogenesis gene expression and the second through FFAR3-dependent gut–brain axis [20•].

Butyrate is a ligand for HCAR2 (also known as GPR109A), a G protein-coupled receptor with anti-inflammatory activity [21,22]. The activation of HCAR2 by nicotinic acid, a known agonist for this receptor, reduces the production of TNF-α, IL-6 and monocyte chemoattractant protein-1 in monocytes [21]. The identification of butyrate as a HCAR2 agonist highlights its potential as a modulator of chronic low-grade inflammatory status, one of the central hallmarks of CMD.

Figure 1



Role of butyrate in colonocytes metabolism and schematic overview of receptors activation by short-chain fatty acids (SCFA). **(a)** Butyrate produced from microbial fermentation of dietary fibre is transported into the colonocytes where it is metabolised as major source of energy via TCA cycle. Butyrate also promotes hyperacetylation of histone protein by acting as HDAC inhibitor. SCFA bind to Free-Fatty Acid Receptors, causing the dissociation of the heterotrimeric G-protein complex into Gαi/q (for FFAR2) **(b)** or Gαi (for FFAR3) **(c)** and Gβγ subunits. Gαi inhibits adenylate cyclase (AC) activity and decreases intracellular cAMP levels, with a resulting reduction in protein kinase A (PKA) activity. The inhibition of PKA activity leads to a decreased phosphorylation of CREB, therefore regulating the transcription of downstream genes. The Gαq pathway activates phospholipase-Cβ (PLC-β) which catalyses the cleavage of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG). IP3 binds to IP3 receptors (IP3R) on the membrane of endoplasmic reticulum (ER) and increases the cytosolic Ca^{2+} concentration. Ca^{2+} and DAG also synergistically activate protein kinase C (PKC). Part of illustrations was designed using Servier Medical Art used under CC BY 3.0.