

Review

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Posted Date: 22 October 2025

doi: 10.20944/preprints202510.1753.v1

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Review

Recycling of Undigested Proteins Provided by the Host to the Large Intestine Microbiota: Implication for Intestinal Bacterial Anabolism, Growth, and Physiology

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Abstract

Although the digestion of dietary and endogenous proteins by the exocrine pancreatic proteases and peptidases in the small intestine luminal fluid is highly efficient for most proteins, it has been approximated that between 3 and 11 g of proteins and peptides are transferred from the small to the large intestine in humans. Here, the proteins and peptides are degraded by the bacterial proteases and peptidases, releasing amino acids in free form. These amino acids are utilized by the abundant population of bacteria, notably amino acids that the bacteria are unable to synthesize, and which can thus be considered as indispensable for these microorganisms. The metabolism of amino acids by colonic bacteria is related to the synthesis of proteins while some specific amino acids are used for DNA and RNA synthesis and in catabolic pathways allowing ATP synthesis and leading to the production of metabolites with documented roles in the metabolism and physiology of both commensal and pathogenic intestinal microorganisms. In the present review, we examine the recycling of undigested host's protein by the large intestine microbiota and the metabolism of amino acids by the intestinal bacteria. We describe in addition how these metabolic pathways are involved in bacterial growth and communication, as well as in bacterial physiology in terms of virulence, resistance to detrimental environmental conditions, and capacity to form biofilms.

Keywords: undigested proteins; intestinal microbiota; metabolic recycling; bacterial anabolism; bacterial physiology

1. Introduction

The intestine of mammals is well known to be inhabited by a complex mixture of microorganisms among which bacteria have been the subject of a vast majority of studies [1]. These microorganisms, which include bacteria, archaea, viruses and fungi are forming the intestinal microbiota. Briefly, archaea is a group of prokaryotes which, based on some of their different molecular, biochemical, and morphological characteristics when compared to bacteria, form a separate domain of the living world than bacteria [2]. Many of the archaea present in the intestinal content are methane-producing archaea called methanogens, which are thus operative to produce methane from hydrogen under anaerobic conditions, as those prevailing in the colon [3,4]. The human intestinal virome is largely dominated by a population of phages which, by infecting specific populations of intestinal bacteria, are one important element implicated in the bacterial composition of the intestinal microbiota [5,6]. Fungi, although representing a minor component of the microbiota, are eukaryotic organisms which can be involved in a competitive relationship with bacteria in the human gut [7]. Lastly, although classically not being considered as a part of the intestinal microbiota,

protozoans in the intestine are eukaryotic organisms belonging to the group of protists, and as such, are components of the gut ecosystem [8].

In healthy individuals, the relatively rapid transit of the luminal content through the small intestine does not allow the development of a large concentration of bacteria in the proximal parts of the small intestine. In sharp contrast, the concentration of bacteria greatly increases in the ileum, and in the large intestine (cecum, colon and rectum) [9]. Indeed, in the human colon, the concentration of bacteria represents as much as 10^9 - 10^{12} colony-forming unit (CFU) per g of content. As a result, bacteria in human feces represent more than 50% of the total solid part [10].

The spectacular increase in the number of bacteria in the large intestine luminal fluid is notably related to the much slower transit of the intestinal content in the large than in the small intestine, allowing intense metabolism of the available substrates provided by the host. The transit time in the human colon is rather variable, averaging approximately 60 hours [11,12]. In healthy adults, the luminal contents of the distal parts of the intestinal tract are characterized by a low level of oxygen tension, thus promoting notably the development of large communities of predominant obligate anaerobes [13], coexisting with facultative anaerobes [14].

The substrates available for the growth of bacteria within the colonic fluid are mainly undigested substrates which are transferred from the ileum to the colon through the ileocecal junction [15]. Within the human large intestine, the cecum and the proximal (ascending) colon receive a fluid which is relatively rich in undigested substrates, while the bacteria in the transverse and distal (descending) colon received presumably more limited quantities of substrates, mainly because the available substrates have been already partly used in the more proximal parts of the large intestine. Regarding the protein part of the undigested substances moving from the ileum to the large intestine, although the metabolism of these compounds in the different parts of the large intestine is poorly documented, it appears that protein fermentation occurs mainly within the distal parts of the colon [16,17]. The process of protein fermentation within the large intestine is influenced by numerous parameters including substrate availability, transit time, pH and osmolarity. The ratio of available carbohydrates/proteins represent an important determinant for substrate utilization by the gut microbiota [18], and in humans, the higher the availability of complex carbohydrates (for a given quantity of proteins), the lower microbiota ferments protein [19,20].

When the fermentable carbohydrates are supplied in high amounts to the intestinal microbiota metabolic activity, the nitrogenous substrates are used for bacterial anabolism and bacterial growth. Conversely, proteins are degraded by intestinal bacteria when other sources of energy are scarce. Longer transit time and more alkaline pH are notably associated with higher level of protein fermentation [21,22]. Thus, the carbohydrates/proteins ratio influences the metabolic activity of the intestinal bacteria, and thus the amounts of amino acids metabolized in the different metabolic pathways [23].

2. Origin of Proteins Available for the Large Intestine Microbiota

In the human large intestine luminal fluid, amino acids in free form are usually not the main nitrogenous source directly available for the microbiota, since amino acid absorption by the enterocytes of the small intestine represents a highly efficient process [24]. Then, few amino acids are transferred from the small to the large intestine through the ileocecal junction [25]. Indeed, in the large intestine, the amino acids originate mainly from the proteins that have not been digested or not fully digested in the small intestinal content [26]. Dietary protein digestion is overall an efficacious process with digestibility in the small intestine being in most cases equal or even higher than 90% [27,28]. However, some proteins from dietary origin are more resistant to the digestion by the catalytic activities of proteases secreted by the exocrine pancreas. These proteins include for instance gluten which is relatively resistant to digestion [29]. It has been estimated from clinical studies performed in the last decades that between 1.5 and 5 g of nitrogen are transferred every day from the small to the large intestine [30–33]. Of note, the nitrogenous material found in the distal small intestine is not only originating from the diet, but for a major part from endogenous sources. In fact,

it has been approximated that roughly 40% of the nitrogenous material transferred to the large intestine originate from alimentation, while the remaining 60% originate from the endogenous compartment [25]. Such nitrogenous material is not constituted exclusively by proteins and peptides, but also, although to a much lower extent, by amino acids (approximately 10%), and by minor quantities of urea and ammonia [33].

By using a classical conversion factor between nitrogen and proteins equal to 6.25, by estimating, as explained above, that 40% of the nitrogenous material transferred to the large intestine originates from undigested dietary proteins, and by considering that 90% of the nitrogenous material is made by proteins and peptides, it can be roughly estimated that approximately between 3 and 11 g of alimentary proteins escape digestion in the small intestine. This estimation fits rather well if we consider the mean protein consumption in geographical areas like European countries and the USA, which averages 85 g/day in adults [34,35], and the mean dietary protein digestibility in the small intestine with an average value of 90%. Indeed, from these data, we can calculate that an average value of 8.5 g of alimentary proteins would be recovered within the large intestine, a value in the 3-11 g range as calculated above [36].

3. Metabolism of Proteins by the Large Intestine Bacteria

3.1. Degradation of Proteins by the Bacterial Proteases and Peptidases and Transport of Peptides and Amino Acids in Bacteria

In the large intestine, the bacterial proteases and peptidases release amino acids from the luminal proteins [37]. Bacteria are equipped with a highly diverse set of proteases present in many common gut bacterial species such as *Clostridium* spp., *Bacteroides* spp., *Lactobacillus* spp. and many others. In fact, hundreds of different proteases have been identified in these bacterial species [38]. Some bacteria, such as lactic acid bacteria, have developed proteolytic systems which compensate for their limited or absent capacities to synthesize several amino acids [39]. Proteolytic systems in lactic acid bacteria gather both extracellular and membrane bound proteases (notably PrtP and CEP) that convert proteins into oligopeptides, and these processes are followed by importation into the bacterial cells via peptide transporters such as Opp, Dpp, and Dtp for oligopeptides, dipeptides, and di- and tripeptides, respectively. Finally, numerous intracellular peptidases in bacteria degrade the oligopeptides into shorter oligopeptides and amino acids in free form [40].

Amino acids and their derivatives can also be both imported and exported from the bacterial cells via transmembrane proteins, including the ATP-dependent ABC transporters, different families of channel proteins, and secondary carriers relying on the proton-motive force, ionic sodium motive force, and solute-solute exchange [41–43]. These amino acid and oligopeptide transporters have been notably studied in *Escherichia coli* [44]. The uptake of amino acids by the large intestine bacteria requires a significant fraction of the available metabolic energy, and as shown in lactic acid bacteria, the metabolic energy cost of amino acid uptake can be reduced by accumulating oligopeptides instead of the individual amino acids, followed by proton-motive-generating efflux of amino acids accumulated in excess in bacteria compared to metabolic needs [45]. The export of amino acids from intestinal bacterial cells into the luminal fluid may represent a way to supply amino acids to other bacterial species, thus representing a process of metabolic cooperation between different bacterial species.

The metabolic fate of amino acids present in free form in the large intestine luminal fluid has been studied. Although some measurable transfer of amino acids across the rodent colonic mucosa has been measured in vivo [46], amino acids, in sharp contrast with the situation prevailing in the small intestine, are not believed to be absorbed to any significant extent by the mammalian colonic epithelium [47–49], and if this proposition is correct, this means that amino acids entering the large intestine are almost lost for utilization by the host for protein synthesis and for utilization in other metabolic pathways [50].

However, some experimental arguments suggest that some amino acid absorption through the mammalian large intestine epithelium cannot be totally excluded [51]. Firstly, in the pig model, infusion of proteins or amino acids into the large intestine lumen indicate whole body N balance improvement which may suggest some amino acid absorption [52]. Furthermore, some absorption of amino acids from microbial origin through the pig colon has been suggested based on the appearance of ^{15}N -labeled amino acids in the venous blood after infusion of ^{15}N -labeled bacteria into the cecum [53]. In addition, some biochemical data indicate the presence of the ATBo+ neutral and cationic amino acid transporter in the colon [54], these transporters being localized at the apical pole of colonocytes [55]. Another neutral and cationic amino acid transporter, namely Bo+ system is expressed on the apical surface of colonic absorptive cells [56]. The hypothesis that some amino acids available within the large intestine luminal fluid would be used for local protein synthesis within the colonic epithelial cells is a possibility that has been little evaluated [57]. In the pig model, during the neonatal period, some amino acid absorption by the colon epithelium has been measured [58,59], suggesting a transient colonic absorption of amino acids in this experimental model.

Finally, it appears from the available data that amino acids within the colon large intestine luminal fluid in adults are kept available, presumably for their most part, for the metabolic activity of the microbiota in relationship with their growth and physiology as will be detailed in the following chapters of the present review.

3.2. The Indispensable Amino Acids for Intestinal Bacterial Species

The definition of indispensable amino acids in mammals (including humans) is related to the fact that among the amino acids required for metabolism and physiological functions in the tissues and organs, nine of them (namely isoleucine, leucine, valine, lysine, methionine, phenylalanine, threonine, tryptophan, and histidine) must be obligatory provided by the diet to meet the body's requirement [60,61]. In other words, indispensable amino acids are those which cannot be synthesized in the body, or cannot be synthesized to any significant extent, when compared to the metabolic and physiological needs.

By analogy with the definition of indispensable amino acids in animals, it is tempting to propose the use of the same terminology with some nuances for the intestinal bacteria. Indeed, not all bacteria within the large intestine are able to synthesize the 20 usual amino acids and the two unusual amino acids (namely selenocysteine and pyrrolysine) they need for protein synthesis and for utilization in other metabolic pathways which are central for bacterial growth and physiology [23]. The amino acids which cannot be synthesized by the intestinal bacteria or cannot be synthesized in significant amount to cover the requirement must be supplied from the luminal fluid and imported within the bacterial cells.

Then, by deduction, the non-indispensable (or dispensable) amino acids for the large intestine bacteria are those which can be synthesized in sufficient amount to cover their metabolic and physiological requirements. The studies of amino acid biosynthesis in intestinal bacteria have been historically focused on few bacterial species including notably *Escherichia coli*, including the enterohemorrhagic *E. coli* (EHEC) which is responsible for severe colonic infection [62], *Salmonella typhurium*, a pathogen known to provoke diarrhea and inflammation in ileum and colon [63], and *Bacillus subtilis*, which is present in the human gut, and which have shown some protective effects in *Citrobacter rodentium*-associated colitis [64]. Obviously, the available data related to these few bacterial species cannot be considered as representative of amino acid anabolism for all the bacterial species present within the large intestine. With this reservation in mind, many of the metabolic pathways at the basis of amino acid metabolism are relatively well conserved across the bacterial lineages. The description of the metabolic pathways involved in the biosynthesis of the 22 amino acids in bacteria is outside the scope of this review but can be found in recent reviews dedicated to this topic [23,38].

The diversity of the metabolic capacities for the different bacteria living in gut can be illustrated by some typical examples. *Clostridium perfringens*, a common human enteropathogen [65] lacks for

instance one or several genes involved in glutamate, arginine, histidine, lysine, methionine, serine, threonine, aromatic, and branched-chain amino acid biosynthesis [66], thus depending on the presence of these amino acids in the surrounding media for all the biochemical pathways involving amino acids, including protein synthesis. Then, these amino acids can be considered as indispensable for *Clostridium perfringens*.

Regarding *Lactobacillus johnsonii*, a human gut commensal [67], this bacterium also appears unable to synthesize almost all amino acids, due to the lack of complete biosynthetic pathways, thus exhibiting dependence on most amino acids either in free form or supplied in peptidic forms in the media [68]. Other bacteria, like *Campylobacter jejuni*, a foodborne pathogen which causes inflammation and enteritis in humans [69] and *Enterococcus faecalis* strains, which are resident intestinal bacteria associated with invasive infections and inflammatory bowel diseases [70], do not contain the whole biosynthetic pathways for some amino acids [71].

Here, it is important to recall that the sole presence of genes within a bacterial genome is not sufficient to establish their functionality [38]. For instance, the genes for all the 20 common amino acids have been identified in the bacterium *Lactococcus lactis*, a noninvasive and nonpathogenic organism [72], but despite this result, several amino acids, namely isoleucine, valine, leucine, histidine, methionine, and glutamate, need to be supplied to this bacterium for growth. This is because several genes coding for several enzymes involved in the biosynthetic pathways of these amino acids are nonfunctional due to point mutations [73,74]. This is also the case for *Staphylococcus aureus*, a common colonizer of the human gut [75], since two strains exhibit auxotrophy for arginine, valine, leucine, cysteine, and proline, despite the presence of the complete sets of genes corresponding to the different biochemical pathways responsible for the biosynthesis of these amino acids in the two strains studied [76]. Thus, for these bacteria, the five amino acids listed above can be considered as indispensable.

3.3. Utilization of Amino Acid for Macromolecule Synthesis in Bacteria

Amino acids in bacteria are well known to be utilized for the synthesis of macromolecules including not only proteins, but also for RNA and DNA synthesis (the main pathways for the metabolism of amino acids by the intestinal bacteria are summarized in Figure 1). To face changing environment, bacteria depend on strictly coordinated proteostasis networks that finally control processes such as the rates of protein synthesis and degradation [77]. One critical mechanism that is involved in the response of bacteria to changing environment (including changes in the concentrations of nutrient in the environment), is represented by the control of the expression of genes at the level of proteosynthesis. At each of the three major steps of translation, namely initiation, elongation, and termination, bacterial cells can tune the translation rate and thus the intracellular protein concentrations depending on their environment [78]. Of note, protein synthesis and protein turnover are dependent on post-translational modifications of a group of bacterial proteins [79].

Regarding RNA and DNA synthesis, three amino acids, namely glycine, aspartate, and glutamine, are used as precursors for the synthesis of the purine and pyrimidine rings. The metabolic pathways involved in pyrimidine biosynthesis from amino acids has been for instance studied in numerous bacterial species, and the results have shown that the synthesis of pyrimidines requires carbamylphosphate as a precursor. In *Escherichia coli*, *Salmonella typhimurium*, and other bacterial species including *Pseudomonas aeruginosa* (present in the human intestinal tract [80]) and *Proteus mirabilis* (which is associated with inflammation in Crohn's disease [81]), carbamylphosphate is synthesized from glutamine and bicarbonate in an ATP-dependent reaction. In the first step of pyrimidine synthesis, carbamylphosphate and aspartate are condensed to form carbamylaspartate. This latter metabolite is then the precursor for uridine triphosphate and cytidine triphosphate in six and seven steps, respectively [82]. Interestingly, the pool of intracellular nucleotides in bacteria ultimately regulate protein synthesis at various stages of this process [83], showing interrelationships between the different metabolic pathways.

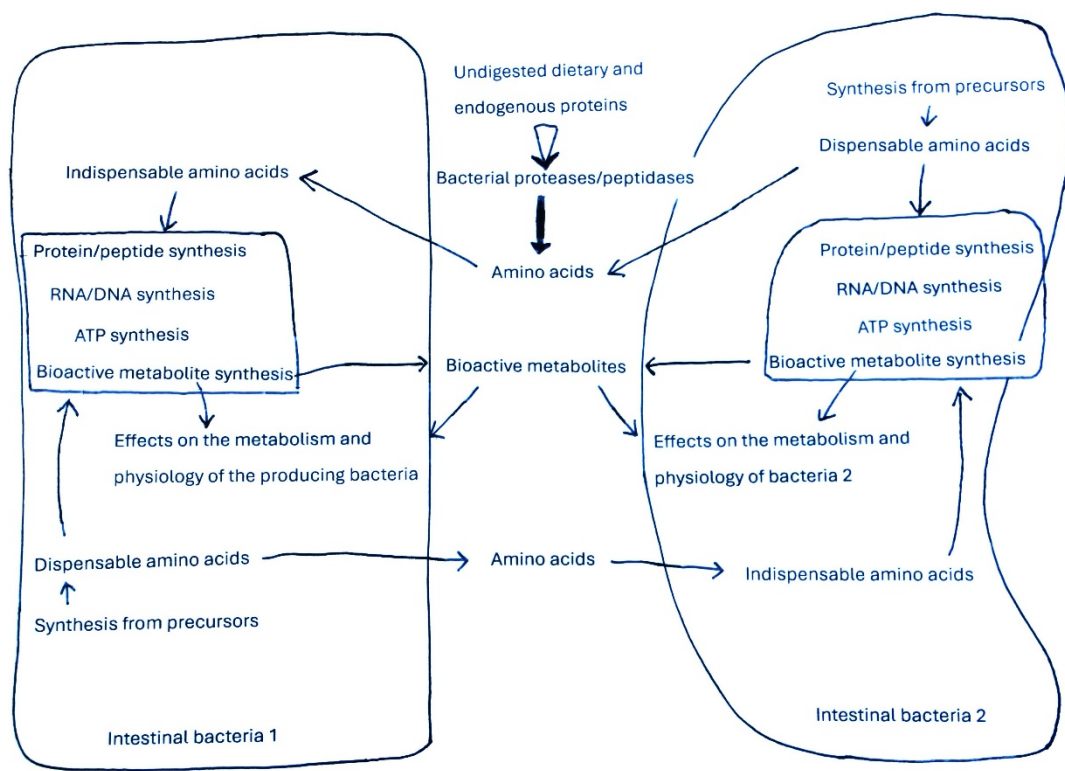


Figure 1. Schematic view of the metabolism of amino acids by the intestinal bacteria. Undigested dietary and endogenous proteins supplied by the host are degraded into amino acids by the bacterial proteases and peptidases. Amino acids can then be transported inside bacteria and serve together with the amino acid synthesized within the bacteria for the synthesis of proteins. The synthesis of RNAs and DNA requires specific amino acids while several amino acids can be utilized for ATP production and for the synthesis of bioactive metabolites. These latter amino acid-derived metabolites can exert effects on the metabolism and physiology of the producing bacteria (bacteria 1). The amino acids which cannot be synthesized by bacteria 1 can be considered as indispensable for these bacteria and thus need to be imported from the medium. Some among the bioactive metabolites generated by bacteria 1 can be exported in the medium and act on the metabolism and physiology of other bacterial species (such as bacteria 2). Of note, some amino acids synthesized by bacteria 1 can be exported in the media and used by bacteria 2 (and vice versa) thus indicating potential metabolic cooperation between different members of the intestinal bacterial community.

3.4. Utilization of Amino Acids for ATP Synthesis in Bacteria

Under aerobic conditions, some bacterial species can convert amino acids to their α -ketoacids counterparts via transamination and deamination reactions. These α -ketoacids are then oxidized in the citric acid cycle. In addition, some bacteria are equipped with a branched-chain keto acid dehydrogenase complex that yields ATP from the oxidized form of the branched-chain amino acids [84]. However, under strict anaerobic conditions, such as the one which prevails in the colon, or in the absence of suitable electron acceptors, strict or facultative anaerobic bacteria such as Clostridia and Fusobacteria can utilize amino acids as energy sources, thus fermenting amino acids in a wide range of reactions including transamination, oxidation, and reduction [85,86]. Thus, in the absence of oxygen and of other inorganic electron acceptors, the substrates for fermentation are used both as electron donors and as electron acceptors, thus resulting in low yield ATP production when compared to the yield of ATP production under aerobic conditions [87]. Many electron donors and acceptors can participate in the different biochemical pathways involved in protein fermentation, including α -ketoacids, molecular hydrogen (H_2), as well as amino acids [88,89]. Bacterial amino acid

fermentation results in the production of metabolic end products, including mainly short- and branched-chain fatty acids [84].

In addition, bacteria such as Lactic acid bacteria can use amino acid decarboxylation to generate ATP [90,91]. Amino acid decarboxylation presumably supports ATP production in condition of adverse environmental conditions. For instance, tyrosine decarboxylation in bacterial species equipped with this metabolic pathway results in the production of tyramine and carbon dioxide (CO₂), and allows the production of ATP by a proton motive force composed of a pH gradient formed during proton consumption in the decarboxylation reaction, and by membrane potential, which itself results from electrogenic transport of tyrosine in exchange for tyramine [92].

In *Clostridium* species, including *Clostridium difficile*, specific metabolic pathways grouped under the name of Stickland metabolism is central for ATP production. Stickland reactions involves the coupled oxidation and reduction of two amino acids, with one amino acid acting as an electron donor, while another amino acid acts as an electron acceptor, then facilitating the production of ATP by substrate-level phosphorylation, and by maintaining the NADH/NAD⁺ pool [93]. The most efficient electron donors include amino acids such as alanine, valine, leucine, and isoleucine, while the most efficient electron acceptors include proline, glycine, and leucine [94]. Ornithine, a non-proteogenic amino acid can undergo Stickland metabolism to yield acetyl CoA, ammonia, and alanine, or can be alternatively converted to proline [95], thus participating in the production of ATP in the bacterial species equipped with these metabolic capacities. Stickland amino acid reactions are believed to provide metabolic resources to support bacterial growth when other substrates, such as carbohydrates, are in short supply [96].

Of note, amino acid utilization for ATP production may be operative in a preferential manner when compared to other ATP-producing substrates. For instance, *Clostridium sticklandii*, a non-pathogenic proteolytic clostridium, which is known to be dependent on amino acids for growth, is considered as a specialist for amino acid degradation. This bacterium has been studied in detail for its metabolic capacity to degrade amino acids thus allowing ATP production [97]. *Clostridium sticklandii* is characterized by numerous transporters for oligopeptides and amino acids, and with a battery of proteolytic enzymatic activities. This bacterium preferentially utilizes the amino acids arginine, threonine, cysteine, serine, and glycine for ATP production.

Interestingly, several amino acids are used by some bacterial species in specific conditions of growth. For instance, lysine degradation, which ends with the synthesis of butyrate, represents a major source of ATP for *Clostridium sticklandii* only in stationary growth phase.

3.5. Utilization of Amino Acids for the Synthesis of Bioactive Metabolites in Bacteria and Effects of These Compounds on Bacterial Growth and Physiology

Numerous amino acid-derived metabolites produced by different intestinal commensal and pathogenic bacteria have been shown to be active on their own metabolism and physiology, with associated effects on their virulence and growth capacities [98]. In addition, from recent studies, emerging roles of several amino acid-derived metabolites released in the surrounding media by some bacterial species have been presumed to act on other bacteria species, thus suggesting that amino acid bacterial metabolism may be involved in the regulation of bacterial physiology and likely as a means of communication between bacteria in different ecosystems.

Amino acid-derived polyamines facilitate bacterial growth, modulate bacterial virulence, promote bacterial acid resistance, and regulate biofilm formation

Polyamines are small aliphatic amines that are produced by bacteria primarily from amino acids. The main polyamines synthesized by bacteria are putrescine, spermidine, agmatine and cadaverine, but numerous polyamine derivatives are produced from these polyamines, and for several of them, by pathways that are not operative in eukaryotic cells [99,100]. Putrescine and spermidine are generally the most common polyamines found in bacteria, while agmatine and cadaverine are found at lower concentrations and spermine is rarely detected in most bacterial species [101]. Polyamines have been measured in the intestinal contents at concentrations from micro- to millimolar

concentrations [1]. A part of polyamines within bacteria is associated with RNA, and such association is paralleled by effects of polyamines on transcription and translation [102–104]. The precursors for putrescine and spermidine synthesis in bacteria are the amino acids ornithine, arginine, and methionine, while agmatine is produced from arginine. Regarding cadaverine, this polyamine is produced from lysine [101]. The conversion of putrescine into spermidine requires the decarboxylated form of the methyl donor S-adenosylmethionine (Figure 2).

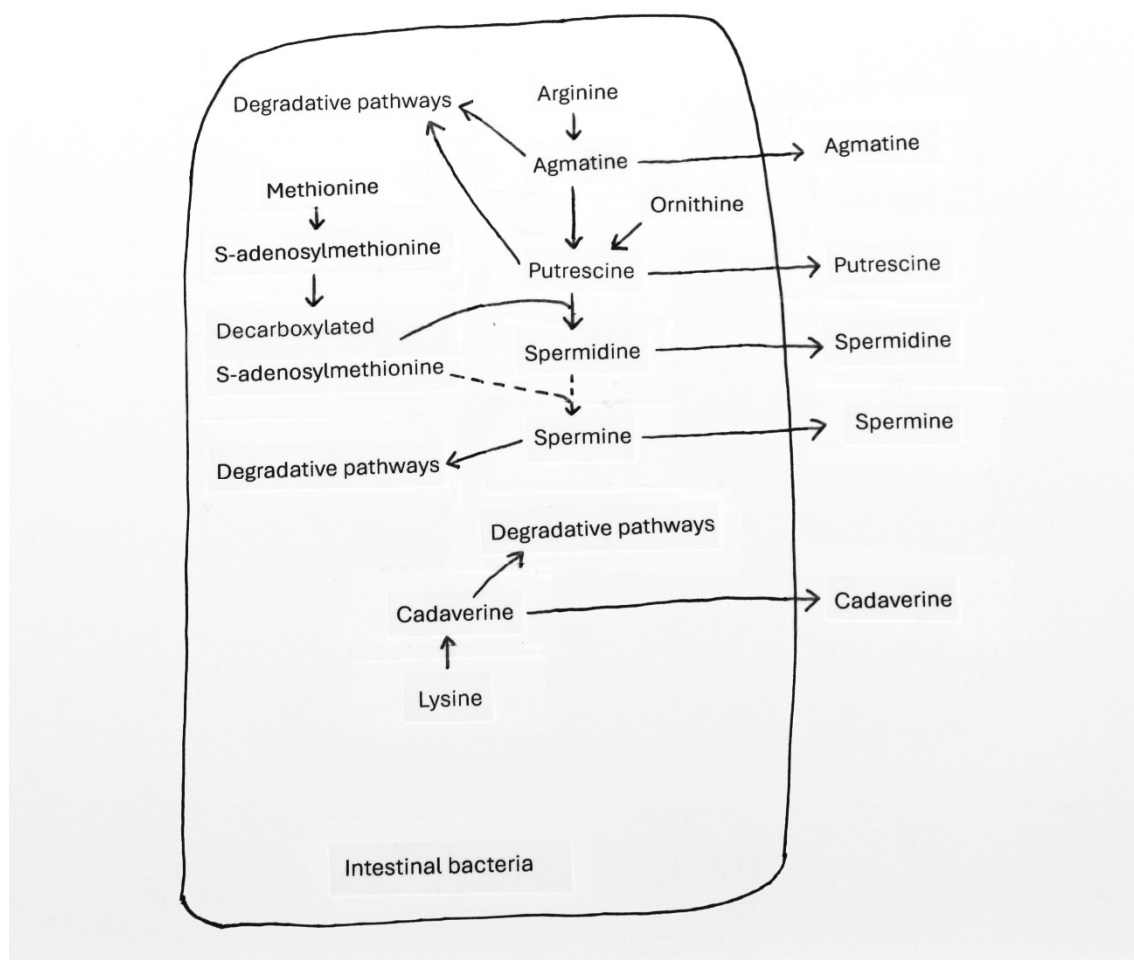


Figure 2. Schematic view of the metabolism of polyamines by the intestinal bacteria. Arginine is the precursor for the synthesis of agmatine, while agmatine and ornithine are the precursors of putrescine. Putrescine and the methionine-derived metabolite decarboxylated S-adenosylmethionine are the precursors for the synthesis of spermidine, and to a lower extent of spermine. Lysine is the precursor of cadaverine. The concentrations of polyamines within bacteria are the net result of synthesis, degradation, uptake, and release in the medium. Polyamines can exert effects on the metabolism and physiology of the producing bacteria. Polyamines released in the medium can be taken up by other bacterial species where it can exert metabolic and physiological effects.

However, not all bacteria are equipped with the metabolic machinery allowing polyamine biosynthesis from amino acid precursors, thus indicating that these bacterial species may be dependent on the import of the polyamines present in the media [105]. These polyamines are likely originating from the polyamines synthesized and released by other members of the bacterial community. In fact, systems of polyamine uptake and release have been identified in numerous bacterial species. For instance, agmatine-putrescine antiporters have been characterized in *Enterococcus faecalis*, and such antiporters is used for importing agmatine and exporting putrescine [106]. Polyamine degradation pathways represent another important player in fixing the polyamine

concentrations within the bacteria intracellular medium [107]. Thus, polyamine concentrations in bacteria are the net result of endogenous synthesis, import, export, and degradation of polyamines.

Polyamines participate in critical physiological functions in intestinal bacteria. The effects of polyamines on bacterial growth are rather heterogeneous depending on the species studied. For instance, *Escherichia coli* rendered deficient for polyamine synthesis can still grow, albeit at reduced rate, when compared with the wild-type counterpart, thus indicating that polyamines are not strictly required for growth of this bacterium [108]. Likewise, in the foodborne pathogen *Salmonella enterica*, polyamines depletion reduces but do not suppress bacterial cell growth [99]. In contrast, polyamine biosynthesis is essential for the growth of the pathogen *Pseudomonas aeruginosa* and of the foodborne pathogen *Campylobacter jejuni* [109,110].

Spermidine can modulate the production of bacterial toxins. Indeed, this polyamine reinforces for instance the production of colibactin [111]. Regarding cadaverine, this polyamine can attenuate virulence and reduce enterotoxin activity in *Shigella spp.* (Maurelli PNAS 1998). In addition, putrescine, cadaverine, spermidine, and spermine have been shown to modulate the virulence of *Vibrio cholerae* [112].

Polyamines can be incorporated into bioactive compounds, notably into bacterial siderophores. These compounds are secreted by bacteria and then scavenge iron in the extracellular medium; this latter compound being then supplied to bacteria via specific receptors [113]. Spermidine and cadaverine can be linked covalently to peptidoglycans, and this process presumably increase bacterial cell wall rigidity [114]. Cadaverine has been demonstrated to provide to *Escherichia coli* and to the foodborne pathogen *Vibrio parahaemolyticus* a mechanism involved in acid resistance [115,116].

Lastly, polyamines are involved in the regulation of biofilm formation. Briefly, biofilms can be viewed as a mixture of high-density bacterial (and archaeal) community contained within a self-producing protective matrix made of polysaccharides, proteins, nucleic acids, and lipids [117,118]. Such structures represent an important element for the modulation of bacterial growth in changing environment, like the situation which may happen in the large intestine [119]. Biofilms are found in intestine where elements of the intestinal microbiota contained within these structures are in close contact with the intestinal mucosal surface [120]. Research on biofilms is motivated by the fact that microorganisms (including the intestinal pathogens) in biofilms become much more resistant to antimicrobial treatment [121]. Biofilm development and quorum sensing have been shown to be interconnected [122,123]. In a few words, quorum sensing enables bacteria to collectively modify their behavior in response to changes in the cell density and species composition within the local environment [124]. The implication of different polyamines in the regulation of biofilm formation, either positive or negative, has been recently documented. The polyamine agmatine is involved in the process of biofilm formation in *Bacillus subtilis* [125]. Another polyamine, namely the uncommon polyamine norspermidine induces biofilm formation in association with increased cyclic di-GMP synthesis, this latter compound being able by itself to activate in *Vibrio cholerae* the expression of genes involved in the formation of biofilm components [126]. In an intriguing and interesting way, norspermine appears to act on *Vibrio cholerae* via a norspermidine sensor [127]. It has been confirmed that norspermidine biosynthesis is required for biofilm formation by *Vibrio cholerae* [128]. In contrast, spermine inhibits *Vibrio cholerae* biofilm formation [129]. The results presented above indicate that different polyamines can exert opposite effects on the bacterial capacity to form biofilms. The respective roles of the different polyamines (either synthesized endogenously by bacteria or taken up from the extracellular media) for the regulation of biofilm formation by different bacterial species among the intestinal microbiota remain unclear, thus requiring additional experimental works.

Cysteine-derived hydrogen sulfide increases bacterial respiration and growth, promotes biofilm formation, and modulates the effects of different antibiotics

Hydrogen sulfide (H₂S) is produced in bacteria from different S-containing substrates including notably cysteine and inorganic sulfate [130]. Cysteine-degrading bacteria in gut include *Fusobacterium*, *Clostridium*, *Escherichia coli*, *Salmonella*, *Klebsiella*, *Streptococcus*, and *Enterobacter* which convert cysteine to H₂S through the catalytic activity of cysteine desulfhydrase [131–133]. Sulfate-

reducing bacteria include the following gut bacteria: *Desulfobrio*, *Desulfobacter*, *Desulfobulbus*, and *Desulfomaculum* [134–136]. *Desulfovibrio* represents the dominant genera of sulfate-reducing bacteria in intestine [137–139]. The amount of sulfate in the diet, as well as the capacity of the small intestine to absorb this compound appear to represent the main parameters which determine the amount of sulfate being transferred to the large intestine [140]. In volunteers, the ingestion of sulfate in supplement increases the fecal sulfide production rate [141]. It appears that overall, current concentrations of sulfate in the large intestine are adequate to support the growth of sulfate-reducing bacteria.

H₂S in the colonic luminal fluid can exist in three forms: the H₂S gas that is partly dissolved in the aqueous phase and represents a highly diffusible compound, hydrosulfide anion (HS⁻) and sulfide ion (S²⁻), this latter compound being present at a negligible level. Indeed, in the aqueous phase, H₂S dissociates into HS⁻ and S²⁻ and H⁺ with pK_a values being 7.04 and 11.96, respectively [142,143]. In healthy subjects, the pH at the colonic mucosal surface ranges between 7.2 and 7.5 in the descending colon and the rectum [119]. Thus, by considering a pH equal to 7.4, approximately one third of sulfide is in the form of H₂S at equilibrium, while two-third are in the form of hydrosulfide anion. However, if the pH becomes more acidic, the H₂S/HS⁻ ratio increases in the large intestine. The concentrations of total H₂S measured in the colonic luminal fluid are rather divergent according to the technics used, ranging from high micromolar to low millimolar concentrations [1]. Measurement in the feces obtained from human volunteers, indicate that 8% of sulfide is in the unbound form [144]. The identification of the compounds which bind sulfide in the colonic lumen, although obviously not exhaustive, points out several compounds from dietary origin that are not fully absorbed in the small intestine. These compounds include zinc [145], heme [146], and polyphenols [147].

Incidentally, H₂S is involved as a precursor for the synthesis of cysteine and methionine in bacteria, and then, such anabolic pathways in gut bacterial species may influence sulfide concentration within the intestinal content. In bacteria, the synthesis of cysteine is made from serine in two steps, with the first step being catalysed by serine acetyltransferase in the presence of the co-substrate acetyl CoA, and the second step is then catalysed by cysteine synthase using H₂S as co-substrate [148,149]. Not all bacteria are equipped with cysteine synthase, since for instance, *Bifidobacterium longum*, which is one of the most abundant bacteria in the infant and adult intestine [150], lacks the corresponding gene and may use alternative pathways involving succinylhomoserine and H₂S as substrates for cysteine synthesis [151]. Regarding methionine synthesis in bacteria, this amino acid is produced through metabolic pathways which share the first three steps involved in threonine synthesis up to the synthesis of homoserine. Then homoserine is converted to methionine by several different pathways which are operative in different bacterial species. These pathways allow the conversion of O-succinylhomoserine and cysteine to cystathionine or convert O-acetylhomoserine (synthesized from aspartate in four steps) and H₂S (or cysteine) to cystathionine. Cystathionine is then converted to homocysteine, the immediate precursor of methionine in the reaction catalysed by methionine synthase [152,153] (Figure 3).

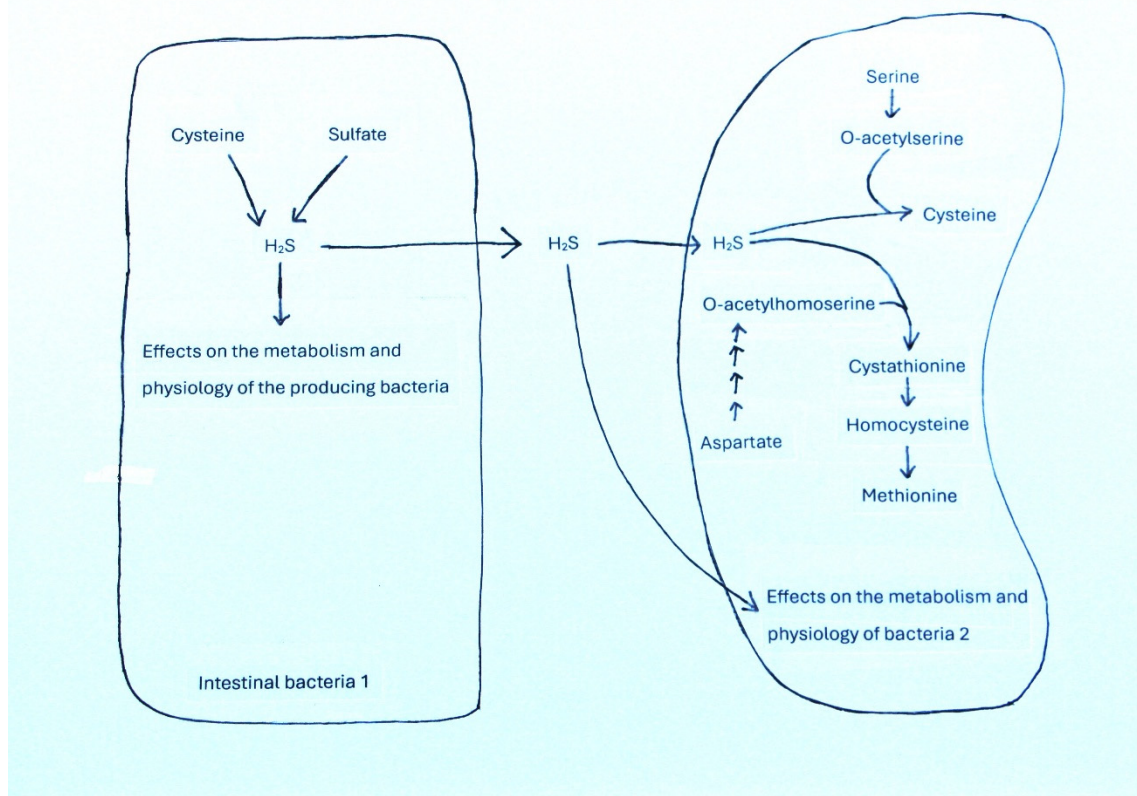


Figure 3. Schematic view of the metabolism of hydrogen sulfide by the intestinal bacteria. Hydrogen sulfide (H_2S) can be synthesized in bacteria mainly from cysteine and sulfate. H_2S can affect the metabolism and physiology of the producing bacteria. H_2S can diffuse from the producing cells and act on the metabolism and physiology of other bacteria (bacteria 2). H_2S can be involved as precursor in the synthesis of cysteine and methionine in the bacteria equipped with the corresponding anabolic pathways.

H_2S , at low concentration stimulates the respiration of the intestinal pathogen *Mycobacterium tuberculosis* and promotes its growth [154]. In contrast, H_2S at excessive concentrations inhibits the terminal oxidase of the respiratory chain of *Escherichia coli* [155], such terminal oxidase representing one element of the supramolecular organization of the bacterial respiratory chain [156]. However, *Escherichia coli* is equipped with alternative bd-type oxidase, which is insensitive to the inhibitory effects of H_2S , and the presence of this isoenzyme allows respiration and growth of this bacterium in H_2S -rich environment [157]. Similarly, cyanide-insensitive oxidase in the intestinal pathogen *Pseudomonas aeruginosa* has been shown to confer tolerance to H_2S regarding its respiration [158]. Thus, it appears that alternative solution for respiration exist in some intestinal bacteria to cope with increased sulfide luminal concentration.

H_2S can also act on some intestinal bacterial species as a protective compound. In the pioneering work of Bachenheimer and Bennett, H_2S produced by *Desulfovibrio desulfuricans* was shown to be the diffusible factor responsible for the protection of *Pseudomonas aeruginosa* from heavy metal toxicity, such as mercury [159]. Incidentally, these important results published more than 6 decades ago indicated that a given bacterial species was able to produce a compound which was active towards another bacterial species. Similarly, H_2S produced by *Escherichia coli* contributes to the protection of *Staphylococcus aureus* against mercuric toxicity [160]. Since these discoveries, but much more recently, in the context of the study of bacterial antibiotic resistance, H_2S has emerged as a protective compound for *Pseudomonas aeruginosa* and *Staphylococcus aureus* against the action of different antibiotics [161,162]. Although the precise mechanisms of action involved in the protective action of H_2S against the effects of antibiotics are not yet known, several experimental results have begun to shed light on these mechanisms. In fact, sequestration of Fe^{2+} ions by H_2S counteracts oxidative stress triggered by some antibiotics in *Escherichia coli* [163]. Furthermore, H_2S has been demonstrated to be

involved in the maintenance of the bacterial redox homeostasis and to protect pathogenic *Escherichia coli* strains against the oxidative stress triggered by the antibiotic ampicillin [164]. Also of note, cystathionine- γ -lyase has been discovered as the primary enzymatic activity which is responsible for H₂S production in *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and inhibition of this catalytic activity potentiates the efficiency of antibiotics against both bacterial species in invitro and in vivo models of infection [165]. These results suggest that endogenously formed H₂S may participate in the resistance of some bacteria to the effects of some antibiotics.

However, H₂S is apparently not a bacterial amino acid which limits the efficiency of antibiotics against all bacteria present within the intestine. For instance, in *Acinetobacter baumannii*, which incidentally is not an H₂S-producer, H₂S reinforces the effects of several classes of antibiotics [166]. Thus, the H₂S-mediated protection or conversely sensitization to the effects of different antibiotics depends on the bacterial species considered, and likely on the antibiotics used. Finally, in another context, the implication of H₂S in the resistance to infection by pathogenic bacteria has been suggested [167]. In this latter study, the endogenous production of sulfide is apparently involved in the enhanced capacity of intestinal commensal bacteria to counteract pathogen infection.

Regarding the establishment and restoration of colonic microbiota biofilms, H₂S has been shown to intervene in such processes [168]. *Fusobacterium nucleatum* is an H₂S producer, and the production of this metabolite in this bacterial species modulates the virulence and susceptibility to antibiotics [169]. Scavenging of H₂S in several bacterial species (including *Escherichia coli*) which produce this compound potentiates both the bactericidal effects of several active compounds and disrupts the formation of the bacterial biofilms, thus indicating that the endogenous synthesis of H₂S by these species represent one component involved in biofilm formation and presumably the associated resistance to bactericidal agents [170].

Arginine-derived nitric oxide inhibits bacterial energy metabolism and growth, and increases the dispersal of biofilm

Nitric oxide (NO) is produced from the amino acid arginine by nitric oxide synthases found in numerous bacteria [171], including several bacteria found in intestine such as *Bacillus subtilis* and *Lactobacillus fermentum* [172,173]. Nitric oxide, as documented for hydrogen sulfide, is a highly diffusible gaseous compound. Incidentally, it is worth noting that the nitric oxide synthase pathway is not the exclusive way of nitric oxide production in intestinal bacteria. In fact, intestinal bacteria such as *Campylobacter jejuni* and *Pseudomonas aeruginosa* can produce NO in the process of nitrite (NO₂⁻) reduction catalyzed by nitrite reductase [174–176]. NO can also be formed by ammonia oxidizing bacteria, such as bacteria belonging to the *Nitrospira* genus [177], some of them being found in the human intestine [178]. The concentration of NO in the gas phase of the colon has been measured in volunteers and average approximately 20 p.p.m. [179].

NO has been shown to be involved in the control of bacterial growth and in the biosynthesis of several secondary metabolites. Indeed, NO exerts bacteriostatic effects against several intestinal bacteria such as *Salmonella enterica* [180]. NO appears to exert its bacteriostatic action at least partially by inhibiting enzymatic activities involved in bacterial energy metabolism [181]. Apart from these effects on bacterial growth, NO has been involved for the synthesis of secondary metabolite in bacteria. For instance, NO is used as a building block for the synthesis of the 1,2,3 triazole moiety of 8-azoguanine [182], a member of the purine and pyrimidine antimetabolites, but it remains unknown if 8-azoguanine is effectively produced by any bacterial species belonging to the intestinal microbiota. NO intervenes in nitration reactions within bacteria [183]. In fact, rufomycin which is produced by bacteria in a NO-dependent nitration step targets proteolysis in *Mycobacterium tuberculosis* [184].

Lastly, NO allows the rapid dispersal of biofilm macrostructure by mechanisms involving NO-sensory proteins in many pathogenic bacteria including the intestinal pathogen *Vibrio cholerae* [185]. Accordingly, several NO donors have been tested recently on different bacterial species, and the results of these experiments show antimicrobial and antibiofilm effects of these compounds, notably on *Fusobacterium nucleatum* [186]. In the bacterial species *Vibrio parahaemolyticus* which may act as an intestinal pathogen, NO promotes the transcription of the quorum sensing regulatory gene *opaR*

[187]. Although NO emerges as a gasotransmitter which is active on the regulation of biofilm formation, further works are required to test if this compound produced endogenously by intestinal bacteria reaches concentrations within the luminal fluid which are compatible with this effect.

Tryptophan-derived indole diminishes bacterial growth and bacterial virulence

Numerous Gram-positive and Gram-negative bacterial species can produce indole from the precursor tryptophan, notably the intestinal bacterial species *Escherichia coli*, *Proteus vulgaris*, *Clostridium* spp., and *Bacteroides* spp. [188–190]. The indole concentration has been measured in the feces from volunteers, thus reflecting the concentration of indole in the most distal segment of the large intestine, and has been found to range from 0.3 to 6.6 millimolar [1]. Indole diminishes the capacities of bacterial cells for motility and aggregation in *Listeria monocytogenes*; a bacterial species occasionally found within the intestine [191]. Indole is also able to diminish the virulence of intestinal bacterial species such as *Pseudomonas aeruginosa* and *Salmonella enterica* [192,193].

Incidentally, but importantly, indole is also active in diminishing virulence and growth of the fungal species *Candida albicans* [194], a microorganism commonly found in intestine [195]. This discovery reveals a new way of communication between intestinal bacteria and fungi. Lactic acid bacteria are also sensitive to the effect of indole since this amino acid-derived metabolite exerts bacteriostatic effect on these bacteria [196]. Lastly, indole may affect the bacterial metabolism since indole affects toxin production by *Klebsiella oxytoca* [197], a normal resident in the intestine which may become pathogenic according to the environmental context [198].

Tyrosine-derived p-cresol produced by Clostridium difficile gives competitive advantage to this bacterium over other bacteria

The bacterial metabolite *p*-cresol (4-methylphenol) is produced from the amino acid tyrosine by anaerobic bacteria, notably the ones which live in the large intestine luminal fluid [199]. Among these numerous bacteria, specific families of bacteria like *Fusobacteriaceae*, *Enterobacteriaceae*, *Clostridium*, and *Coriobacteriaceae* are active *p*-cresol producers [200,201]. The *p*-cresol concentrations measured in the human colonic contents are in the low millimolar range [1]. Of major interest, the capacity of *Clostridium difficile* to produce *p*-cresol is one important element which gives to this bacterial species a competitive advantage over other gut bacteria such as *Escherichia coli*, *Klebsiella oxytoca*, and *Bacteroides thetaiotaomicron* [202]. *Clostridium difficile* is well known to represent a major cause of intestinal infection and diarrhea in patients following treatment with antibiotics ([203]. Using a mouse model of *Clostridium difficile* infection, it has been observed that excessive *p*-cresol production affects the gut microbiota diversity. Also of note, by removing the capacity of *Clostridium difficile* to produce *p*-cresol, this bacterium was less able to recolonize the intestine after an initial episode of infection [202]. As expected, *Clostridium difficile* can tolerate *p*-cresol concentrations as high as 10 millimolar [204,205].

Tyrosine-derived skatole inhibits biofilm formation by enterohemorrhagic Escherichia coli

Skatole (3-methylindole) is a metabolite produced by bacteria from tryptophan [206,207]. *Lactobacillus*, *Clostridium*, and *Bacteroides* are known skatole producers [208]. Fecal skatole concentrations in healthy individuals are usually relatively low, averaging approximately 40 micromolar [1]. Skatole display a robust capacity to inhibit biofilm formation by the enterohemorrhagic *Escherichia coli* [209].

Glycine-derived betaine protects bacteria against osmotic stress

Although glycine betaine metabolism has been principally studied in bacteria which are not found in intestine, these studies indicate that this compound is derived from extracellular sources and/or from endogenous synthesis from glycine [210,211]. Glycine betaine is used by bacteria for protection against osmotic stress [212]. Notably, glycine betaine is an osmoprotectant in the intestinal bacteria *Pseudomonas aeruginosa* [213]. Such capacity may be relevant in case of increased luminal osmolarity within the colonic fluid [119].

Amino acid-derived glutathione is active against oxidative stress

Glutathione is synthesized from the three amino acids glutamate, cysteine, and glycine by numerous Gram-negative bacteria but only in few Gram-positive bacteria such as *Listeria*

monocytogenes. Glutathione plays a key role in maintaining the proper oxidation state of protein thiols in bacteria and is involved in the response of bacteria to environment creating a situation of oxidative stress [214,215].

Histidine-derived histamine helps bacteria to survive in acidic media

Histamine, mainly known as a biogenic amine involved in the allergic disease, has been demonstrated to act on some bacteria. Production of histamine from the simple decarboxylation of the amino acid histidine has been demonstrated in numerous Gram-positive and Gram-negative bacterial strains [216], notably in bacteria belonging to the intestinal microbiota such as *Pediococcus parvulus*, *Morganella morganii*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Citrobacter freundii*, and *Hafnia alvei* [217]. Recent studies show that histamine can improve the survival of bacteria in acidic condition. Generation of proton motive force by histidine decarboxylation has been demonstrated in *Lactobacillus buchneri* [218]. Furthermore, it has been elegantly shown that by expressing the functional histidine decarboxylase pathway in *Lactococcus lactis*, these bacteria survive longer in acidic medium (pH 3.0) than the control cells counterpart [219]. However, since the pH in the human large intestine content is only slightly acidic or near neutrality, ranging from 5.7 to 6.8 in cecum, while ranging from 6.1 to 7.5 in the descending colon and rectum [220], it remains to be demonstrated if such histamine-dependent capacity of bacteria to survive in acidic medium is relevant for the intestinal bacteria in this range of pH.

Amino acid-derived dopamine, serotonin, noradrenaline, and gamma-amino butyric acid are involved in the regulation of bacterial growth, virulence, and bacterial acid tolerance

Dopamine, primarily known as a neurotransmitter in animals, has been shown to be active on some bacteria. Dopamine is produced by many bacterial species present in the intestine such as *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris*, and *Klebsiella pneumoniae* [221]. Bacterial tyrosinases are the enzymatic activities which catalyse in bacteria the conversion of tyrosine to dihydroxyphenylalanine (DOPA), the direct precursor of dopamine [222]. Dopamine concentration has been measured in the mouse large intestine luminal content, averaging approximately one micromolar [223], but to the best of our knowledge, the concentration of dopamine in the human colonic fluid has not been determined. Dopamine accelerates the growth of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* [224]. Furthermore, dopamine acts as a siderophore-like iron chelator that promotes the growth of *Salmonella enterica* [225].

Serotonin (5-hydroxytryptamine), a compound which is well known to be a neurotransmitter in animals, is produced from the amino acid tryptophan in many intestinal bacterial species among which *Propionibacterium*, *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Streptococcus*, *Bacteroides*, and *Escherichia coli* [217]. Serotonin appears to regulate either positively or negatively, depending on the bacterial species considered, the virulence of different bacteria. Serotonin enhances the virulence of *Pseudomonas aeruginosa* in in vitro and in vivo experiments; the in vivo experiments being performed using a model of rodent infection [226]. In this latter study, serotonin was found to regulate bacterial quorum sensing. As introduced above, quorum sensing is the process by which bacteria communicate, allowing groups of bacteria to synchronously modify the bacterial population density and composition in vicinal community [123].

Noradrenaline (norepinephrine) is produced from the amino acid tyrosine by several intestinal bacteria including *Bacillus subtilis*, *Escherichia coli*, and *Proteus vulgaris* [217]. This compound, known as neurotransmitter in animals, affects bacterial growth either positively or negatively, depending on the bacterial species studied. Noradrenaline is notably active on the growth of the following intestinal anaerobic bacteria: *Klebsiella pneumoniae*, *Fusobacterium nucleatum*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Shigella sonnei*, and *Staphylococcus aureus*. In addition to its effect on bacterial growth, noradrenaline increases the virulence of several anaerobic bacteria such as *Clostridium perfringens* [227–229].

GABA (gamma-aminobutyric acid) is produced from the amino acid glutamate by several bacterial species present in the intestinal luminal fluid such as *Lactobacillus* and *Bifidobacterium* [230–232]. GABA, known as the main inhibitory neurotransmitter in the mammalian brain, is

involved in tolerance of bacteria such as *Bacteroides* spp. to acidic media through the maintenance of the intracellular pH [233,234].

Tyrosine-derived 4-hydroxyphenylacetate inhibits bacterial growth and virulence

The bacterial metabolite 4-hydroxyphenylacetate is a metabolic intermediate which is produced from the amino acid tyrosine by intestinal bacterial species that synthesize phenol and *p*-cresol as metabolic end products [200]. The transport of 4-hydroxyphenylacetate from the extracellular media has been studied in *Escherichia coli* [235], thus raising the hypothesis that this compound would be released by some intestinal bacterial species and taken up by others. This compound inhibits the growth of the foodborne pathogen *Listeria monocytogenes*, an effect which is associated with alteration of the bacterial morphology and with a decrease of the expression of several genes involved in bacterial virulence [236].

Amino acid (and other substrate)-derived organic acids serve as energy substrates in bacteria and modulate their growth and virulence

During the catabolism of amino acids within bacteria, several organic acids, including succinate, oxaloacetate, formate, and lactate, are intermediary or terminal metabolites which may be produced in significant amounts [15,237]. These compounds are obviously not exclusively produced from amino acids but can originate from other substrates like carbohydrates [238,239].

Succinate oxidation by *Escherichia coli* was described more than seven decades ago [240]. Since then, several studies on that topic were performed, including a study showing capacity of *Bacillus lactis* to use succinate for respiration [241]. Succinate can be used by bacteria for ATP and reduced equivalent generation. Succinate is involved in the mycobacteria respiration, serving both as an intermediate in the tricarboxylic acid cycle and as an electron donor for the respiratory chain [242]. Of note, impaired succinate oxidation in the intestinal bacterium *Mycobacterium tuberculosis* prevents its growth, thus pointing out a central role of the oxidation of this metabolite for *M. tuberculosis* proliferation. In this latter bacterium, succinate dehydrogenase, which converts succinate to fumarate, acts as a central regulator of respiration [243]. Succinate produced by the gut microbiota promotes infection by the opportunistic intestinal pathogen *Clostridium difficile* [244], and extracellular succinate induces biofilm formation by this pathogen [245]. Also of major interest, *Clostridium butyricum*, a butyrate-producing bacterium found in the human gut, can prevent the proliferation of *C. difficile* by diminishing the succinate concentration within the large intestine luminal content [246]. Such decreased succinate concentration represents apparently the net result of the overall metabolic activity of the intestinal microbiota, suggesting subtle metabolic communication between intestinal bacteria.

The tricarboxylic acid cycle intermediate oxaloacetate, when produced by *Escherichia coli*, improves the survival of the amoeba parasite *Entamoeba histolytica* in the large intestine luminal fluid [247], thus suggesting bacterial-parasite communication between microorganisms in the large intestine. *Entamoeba histolytica* is the causative agent of human amoebiasis, an enteropathy affecting millions of humans worldwide [248].

Regarding formate, this organic acid is involved in energy metabolism in different bacterial species. Formate enhances respiration in the intestinal bacterial species *Campylobacter jejuni* [249]. However, at excessive concentrations, formate can reduce the growth of several sulfate-reducing bacteria [250], notably the species *Desulfovibrio vulgaris* found in the human intestine. Formate has been demonstrated to be secreted by the intestinal pathogen *Shigella flexneri*, promoting the expression of genes involved in its own virulence [251].

Lactic acid bacteria ferment several substrates predominantly to lactate [252]. Lactate is used as an oxidative substrate and an ATP source by many intestinal bacteria such as *Salmonella* and *Campylobacter* [253,254].

Lastly, concerning citrate, although the tricarboxylic acid cycle is generally not much prominent in bacteria, some intestinal bacterial species such as sulfate-reducing bacteria and *Escherichia coli* can use several amino acids (as well as other substrates), giving rise during their catabolism to the synthesis of metabolic intermediates of the tricarboxylic acid cycle such as oxaloacetate and succinate

(see above), and also of citrate [255,256]. Citrate can also be obtained by bacteria from extracellular sources [257]. Endogenous sources of citrate in bacteria involves citrate synthase which converts oxaloacetate and acetyl-CoA to citrate, while importation from the extracellular media involves citrate transporters [258,259]. Citrate metabolism has been studied in bacterial species such as the intestinal bacteria *Lactobacillus casei*, and the results obtained show that the major metabolic end products formed are pyruvate, lactate, and acetoin [260]. In intestinal bacteria such as *Klebsiella pneumoniae* and *Enterobacter faecium*, citrate represents an oxidative and ATP-producing substrate [257,261]. Citrate metabolism in bacteria is at the origin of the generation of a membrane potential and a pH gradient that are involved in ATP synthesis [262,263]. In addition to its role in bacterial energy metabolism, citrate is a precursor for the synthesis of staphyloferrins. These compounds, which are part of the family of siderophores, enhance bacterial growth under condition of iron restriction [264].

4. Conclusion and Perspectives

The idea that the host is the main supplier of amino acids for the metabolism and physiology of bacteria contained within the intestinal luminal fluid originates from the fact that significant amounts of undigested proteins, either from dietary or endogenous origin, are transferred from the ileum to the large intestine. The utilization of these proteins, after proteolysis by the intestinal bacteria, may be viewed, as we did in the present review, as a form of recycling of amino acids which have not been used by the hosts. These amino acids can be utilized for bacterial metabolism and physiology. Indeed, numerous bacteria of the intestinal microbiota do not possess the metabolic capacity to synthesize the 22 amino acids required for protein synthesis and for utilization of specific amino acids in other metabolic pathways. Thus, these amino acids which must be available from the extracellular medium can be viewed as “bacterially indispensable” for the survival of the intestinal bacteria and for the maintenance of the bacterial mass within the large intestine in a context of regular excretion of bacteria in the feces.

In this paper, we have focused on the effects of the amino acid-derived metabolites which have been shown to be involved in the regulation of the intestinal bacteria growth and in the bacterial metabolism and physiology. A growing number of articles reports on the effects of such bacterial amino acid derivatives on the virulence of the intestinal bacteria, on their capacity to form biofilms, and on their ability to face changing luminal parameters such as osmolarity, pH, and oxidative stress generating environment. Effects of amino acid-derived metabolites on bacterial respiration and energy metabolism have also been reported, and such effects have been in some cases linked with effects on bacterial growth. Also of major interest, recent papers indicate that the metabolism of amino acids within intestinal bacteria leads to the production of compounds which are released in the extracellular medium and which can act on other bacterial species present in the medium, thus revealing new mode of communication between bacteria from different species. From few emerging results presented in this review, it appears that this type of communication is not exclusively related to communication between intestinal bacteria but is also related to communication between intestinal bacteria and other intestinal microorganisms such as parasites and fungi.

The quantities of the amino acid precursors derived from undigested proteins which are available for the metabolism of bacteria in the large intestine luminal fluid represent likely a parameter which will influence the concentrations of the bioactive bacterial metabolites derived from amino acids in this fluid. In support of this concept, it has been shown in a randomized controlled double-blind clinical trial that supplementation with either plant or animal protein (with different amino acid composition but given in the same quantity) in volunteers led to differences in the composition of the amino acid-derived bacterial metabolites in feces and urine [265].

However, some reservations must be formulated regarding the interpretation of the available results and numerous questions need to be answered in future experimental and clinical works. Firstly, most studies have been performed in vitro with intestinal bacteria in a context that often does not fully mimic the conditions that prevail in the large intestine. Secondly, the amino acid-derived

metabolites are often tested at concentrations which may not be the ones that are found in the human large intestine luminal fluid. Of note, the concentrations of bacterial metabolites within the large intestine luminal fluid may for some of them largely diverge among individuals, and further information are needed to determine the proportion of metabolites in their free (presumably bioactive) form and in forms bound to luminal compounds. In addition, the intracellular concentrations of metabolites in intestinal bacteria which are associated with bioactive effects remain unknown in almost all cases. Third, these amino acid derivatives are generally tested individually, thus not representing the complex mixture of these derivatives as found in the large intestine content in real life situation.

These reservations being made, we are facing here an exciting and stimulating area of research in which future works should help to better understand the way amino acid metabolism within the intestinal bacteria influence their growth and physiology, and thus finally the composition of the intestinal microbiota in terms of commensal and pathogenic microorganisms. This will certainly provide precious indications which will prove to be useful in terms of human health from both preventive and curative perspectives.

Funding: This research received no specific funding.

Informed Consent statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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