1. ABSTRACT

Bacteria in the gastrointestinal (GI) tract play an important role in the metabolism of dietary substances in the gut and extraintestinal tissues. Amino acids (AA) should be taken into consideration in the development of new strategies to enhance efficiency of nutrient utilization because they are not only major components in the diet and building blocks for protein but also regulate energy and protein homeostasis in organisms. The diversity of the AA-fermenting bacteria and their metabolic redundancy make them easier to survive and interact with their neighboring species or eukaryotic host during transition along GI tract. The outcomes of the interactions have important impacts on gut health and whole-body homeostasis. The AA-derived molecules produced by intestinal bacteria affect host health by regulating either host immunity and cell function or microbial composition and metabolism. Emerging evidence shows that dietary factors, such as protein, non-digestible carbohydrates, probiotics, synbiotics and phytochemicals, modulate AA utilization by gut microorganisms. Interdisciplinary research involving nutritionists and microbiologists is expected to rapidly expand knowledge about crucial roles for AA in gut ecology and host health.

2. INTRODUCTION

The digestive tract of humans and animals is colonized by dense and highly complex community of microorganisms composed mainly bacteria, whose total number can exceed $10^{14}$ cells (1). The activities of these bacteria have potential effects on host nutrition and health through the metabolism of dietary components and interaction with intestinal epithelial cells. Amino acids (AA), which are major nutrients in the diet, not only support the growth of bacteria and their host but also regulate energy and protein homeostasis in the body (2, 3). It is most probable that the interplay between gut bacteria and dietary nitrogenous substances (especially AA) have important impacts not only on the host’s nutrition (e.g., AA homeostasis) and health but also on the efficiency of dietary AA supplementation (4-7). Recent development of new molecular techniques and concepts broadened our knowledge about the evolutionary and functional aspects of the complex microbial community in the GI tract (8-11). Therefore, AA metabolism in gut bacteria in complex environments ultimately provides a strategy for their survival and growth in the digestive tract, thereby having both positive and negative effects on the host (6, 12). This review highlights the diversity of intestinal bacteria and...
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their species-specific AA metabolism with a special emphasis on interactions among dietary composition, gut environments, and host health.

3. DIVERSITY AND ABUNDANCE OF THE AA-FERMENTING BACTERIA IN THE DIGESTIVE TRACT

The utilization of AA is widely distributed among bacteria residing in the digestive tract of humans and animals. Studies over the last decades mainly focused on AA fermentation in gut bacteria and showed the diversity of AA-fermenting bacteria in the digestive tract (Table 1). Among the AA-fermenting bacteria, strains belong to the Clostridium clusters (including Clostridium spp., Fusobacterium spp., Peptostreptococcus spp., Veillonella spp., Megasphaera elsdenii, Acidaminococcus fermentans, Selenomonas ruminantium) have been extensively investigated. They were identified to be the predominant AA-fermenting microbiota along the digestive tract of humans and animals. It was found that bacteria belonging to Fusobacterium spp., Prevotella spp. and Streptococcus spp. were predominant in the mouth and play important roles in oral health (13). Work on the abundance and diversity of AA-fermenting bacteria in the large intestine of healthy humans indicated that bacteria belonging to the clostridia and peptostreptococci were the most prevalent species using culture-based methods (14). Phylogenetic analysis of the bacterial 16S rRNA gene sequences revealed that bacteria belonging to the Clostridium clusters, the Bacillus-Lactobacillus-Streptococcus group (including Streptococcus spp.) and Proteobacteria (including Escherichia coli and Klebsiella spp.) were abundant in the small intestines of humans and swine (15-21). Such findings suggest that these bacteria might be important in host nutrition and health.

In humans and mono-gastric animals, the numbers of bacteria increase from $10^7$ cells per gram digesta in the stomach to $10^{11}$ cells per gram digesta in the large intestine (19, 22). However, based on the calculations of the existing data, the numbers of AA-fermenting bacteria account for less than 1% of the total bacteria in the large intestine of healthy humans and the rumen (14, 23). Interestingly, the abundance of total bacteria and specific groups of bacteria in different segments of the GI tract could be influenced by the physiological conditions of the gut and dietary factors (1, 14, 22, 24, 25).

4. AA METABOLISM IN GUT BACTERIA

Nutrients, including dietary and host-derived proteins and AA, are used for the growth and survival of bacteria in the digestive tract (1, 26). Biochemically, proteins are first hydrolyzed into peptides and amino acids by various kinds of host- and bacteria-derived proteases and peptidases (23). The released peptides and AA can be further utilized by both gut bacteria and host, although certain bacteria may not use extracellular AA due to a lack of specific transporters. Studies over the last decades showed that many bacteria such as Prevotella ruminicola, Butyrivibrio fibrisolvens, Megasphaera elsdenii, Misukella multiacididas, Selenomonas ruminantium and Streptococcus bovis harbor highly active dipeptidyl peptidase and dipeptidase, suggesting that these bacteria might be important for protein digestion and AA absorption in the mammalian digestive tract (23). Indeed, most gut bacteria utilize AA and ammonia as preferred nitrogen source (23). However, compared to AA and ammonia, peptides are the only preferred nitrogen source in Prevotella ruminicola (27). It was possible that the peptides are first transported into P. ruminicola cells and then utilized by the cells either in the intact form or as free AA derived from peptide degradation (27). Other bacterial species might lack peptide transport systems and thus could only utilize extracellular AA and ammonia (27-31). Overall, peptides, AA and ammonia are either utilized for the synthesis of bacterial cell components or catabolized through different pathways. This diversity of the metabolism of dietary nitrogenous substances in gut bacteria may have either positive or negative effects on the host.

4.1. Incorporation of AA into bacterial cells

The first step of the incorporation of AA into bacterial cells is AA transport. During the early 1980’s and 1990’s, Russell and colleagues conducted series of research investigating the mechanism of AA transport in rumen bacteria (32). It was found that sodium-dependent transport and, to a lesser extent, facilitated diffusion play important role in AA transport by some of the dominant AA-fermenting bacteria (28, 30, 31). However, the transport of glutamine in Streptococcus bovis was likely driven by phosphate-bond energy, i.e. ATP (29). The uptake of arginine and lysine might share the same transporter in Clostridium bifermentans strain SR and the conversion of arginine to ornithine by the bacteria facilitates arginine transport (33, 34). When extracellular pH decreased from 7.5 to 5.5, the transport of arginine declined linearly in strain SR (33). The above findings suggest that gut bacteria use different strategies in the utilization of different AA and nitrogen source whereas the extracellular environment might affect the patterns of bacterial AA utilization.

Much evidence shows that the transport and incorporation of certain AA into bacterial cells vary with AA structure. For instance, the proportions of glutamate plus glutamine, aspartate plus asparagine, lysine, BCAA, threonine, serine and glycine were higher than other AA in the cells of both gram positive and gram negative gut bacteria (Table 2). Similar observations were also found in the mixed bacteria, which simulated the real situations in the digestive tract (Table 2). These findings suggest that the above AA might be “essential” for the optimal growth of gut bacteria. It is of great interest that some of these AA are either nutritionally essential or functionally important to the animals (2). Although it is not clear whether the AA utilized for bacterial protein synthesis was mainly from the assimilation of extracellular AA or de novo synthesis under physiological conditions, the synthesis of bacterial protein is likely important to host nutrition (35, 36). In ruminants, bacterial proteins synthesized in the rumen are digested and the resultant AA or small peptides are absorbed by the small intestine. This process has nutritional advantages...
## Table 1. Major AA-fermenting bacteria in the digestive tract of humans and animals

<table>
<thead>
<tr>
<th>Bacterial species</th>
<th>Preferred AA substrates</th>
<th>Metabolites</th>
<th>Primary origins</th>
<th>Niches</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fusobacteria; Firmicutes; Clostridia; Clostridiales; Clostridiaceae</strong></td>
<td></td>
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<td></td>
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<tr>
<td><em>Fusobacterium nucleatum</em></td>
<td>Arg, Asp, Asn, Glu, Gln, Orn, Thr</td>
<td>Arg (Orn, urea), Asp (Asn, fumarate, oxaloacetate), Asn (Asp, ammonia), Gln (Glu, ammonia), Glu (acetate, butyrate, ammonia, CO₂), Gly&lt;=&gt;Thr, His (urocanate, ammonia, Glu), Lys (3,6-diaminohexanoic acid), Orn (putrescine)</td>
<td>Human</td>
<td>Mouth, small intestine, large intestine</td>
<td>14, 67, 121-123, KEGG Pathway Database</td>
</tr>
<tr>
<td><em>Fusobacterium varium</em></td>
<td>Glu, His, Lys, Ser</td>
<td>Glu (acetate, butyrate, ammonia, CO₂), His (urocanate, ammonia, Glu), Lys (3,6-diaminohexanoic acid), Ser (acetate, lactate)</td>
<td>Human</td>
<td>Mouth, small intestine, large intestine</td>
<td>122, 124, 125</td>
</tr>
<tr>
<td><strong>Proteobacteria; Gammaproteobacteria; Enterobacteriaceae; Enterobacteriaceae</strong></td>
<td></td>
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<tr>
<td><em>Escherichia coli</em></td>
<td>Arg, Asp, Asn, Glu, Gln, Orn, Thr</td>
<td>Arg (Cit, Orn, putrescine, spermine, agmatine, CO₂), Asn (Hun), Pig, Ruminant, Horse, Dog, Monkey, Rodent</td>
<td>Human, Pig</td>
<td>Small intestine, colon, feces</td>
<td>72, 122, 126-131, KEGG Pathway Database</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>Arg, Asn, Glu, Gln, His, Lys, Met</td>
<td>Arg (Orn, putrescine, spermine), Asn (Asp, ammonia), Gln (Glu), Gln (Glu, ammonia), His (urocanate, ammonia, Lys (cadaverine, CO₂), Met (S-adenosyl-L-methionine)</td>
<td>Human, Pig</td>
<td>Small intestine, colon, feces</td>
<td>122, 129, 131, KEGG Pathway Database</td>
</tr>
<tr>
<td><strong>Proteobacteria; delta/betaproteobacteria; Epipodophyllococeae; Campylobacterales; Campylobacteraceae</strong></td>
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<tr>
<td><em>Campylobacter jejuni</em></td>
<td>Asn, Asp, Glu, Gln, Pro, Ser</td>
<td>Asn (Asp, ammonia), Asp (fumarate, ammonia), Gln (Glu, ammonia), Gln (Pro (Glu) Ser (pyruvate, ammonia)</td>
<td>Human, Poultry</td>
<td>Rumen, small intestine, colon, feces</td>
<td>18, 20, 132</td>
</tr>
<tr>
<td><em>Firmicutes; Bacilli; Lactobacillales; Streptococcaceae</em></td>
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</tr>
<tr>
<td><em>Streptococcus bovis</em></td>
<td>Glu</td>
<td>Pyroglutamate, ammonia</td>
<td>Human, Ruminant, Pig</td>
<td>Rumen, small intestine, large intestine</td>
<td>14, 34, 122,133-135</td>
</tr>
<tr>
<td><strong>Firmicutes; Clostridia; Clostridiales; Peptostreptococcaceae</strong></td>
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</tr>
<tr>
<td><em>Peptostreptococcus sp.¹</em></td>
<td>Glu, Leu, Phe, Ser, Thr</td>
<td>Gln (pyroglutamate, acetate, ammonia, CO₂), Leu (isovalerate, isocaproate, ammonia, H₂), Phe (phenylpropionaté, phenyllactate, phenylacetate, ammonia, CO₂), Ser (lactate, malate, acetate, ammonia, CO₂), Thr (propionate, ketobutyrate, butyrate, acetate, lactate, ammonia, CO₂)</td>
<td>Human, Ruminant, Pig</td>
<td>Rumen, small intestine, cecum, colon</td>
<td>18, 20, 132</td>
</tr>
<tr>
<td><strong>Firmicutes; Clostridia; Clostridiales; Clostridiales</strong></td>
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<tr>
<td><em>Clostridium difficile</em></td>
<td>Ile, Leu, Lys, Pro, Thr</td>
<td>Ile and Leu (isovalerate, isocaproate, ammonia, CO₂), Lys (propionate, ketobutyrate, butyrate, acetate, lactate, ammonia, CO₂)</td>
<td>Human, Pig</td>
<td>Large intestine</td>
<td>14, 52, 136,137</td>
</tr>
<tr>
<td><em>Clostridium perfringens</em></td>
<td>Arg, Asp, Asn, Cit, Gln, Glu, GABA, Gly, His, Ser, Thr, Lys, N-methylglycine</td>
<td>Arg (Cit, ammonia, putrescine), Asp (Asn, Ala, fumarate, oxaloacetate), Asn (Asp, ammonia), Cit (Arg), Gln (Glu, ammonia), Glu (Gln, 2-oxaloacetate, GABA, GABA (propylamine, CO₂), His (histamine, CO₂), N-methylglycine (methylamine, CO₂), Ser&lt;=&gt;Gly&lt;=&gt;Thr, Lys (cadaverine, CO₂), Lys (cadaverine, CO₂)</td>
<td>Human, Ruminant, Pig</td>
<td>Stomach, small intestine, colon, feces</td>
<td>52, 66, 69, 128, KEGG Pathway Database</td>
</tr>
<tr>
<td><em>Clostridium ruminantium</em></td>
<td>Glu, Glu, His, Ser, Pyroglutamate</td>
<td>Ammonia, acetate, butyrate</td>
<td>Human, Pig</td>
<td>Rumen, cecum</td>
<td>95, 134, 150, 151</td>
</tr>
<tr>
<td><strong>Firmicutes; Clostridia; Clostridiales; Veillonellaceae</strong></td>
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<tr>
<td><em>Megasphaera elsdenii</em></td>
<td>Ser, Thr</td>
<td>Isobutyrate, 2-methylbutyrate, isovalerate</td>
<td>Human, Ruminant, Pig</td>
<td>Rumen, small intestine, large intestine, feces</td>
<td>14, 18, 146, 147, 148</td>
</tr>
<tr>
<td><strong>Acidaminococcus fermentans²</strong></td>
<td>Asp, Cit, Gln, Glu, His, Orn, Ser, Thr</td>
<td>Asp (fumarate, oxaloacetate), Cit (Arg), Gln (Glu, ammonia), Gln (Glu, acetate, butyrate, CO₂), His (urocanate, ammonia, Orn (Cit, Arg, putrescine, spermine), Spermine, Ser&lt;=&gt;Gly&lt;=&gt;Thr</td>
<td>Human, Ruminant, Pig</td>
<td>Small intestine, large intestine, feces</td>
<td>123, 148, 149, KEGG Pathway Database</td>
</tr>
<tr>
<td><strong>Bacteroides/Chlorobi group; Bacteroidetes; Bacteroidia; Bacteroidales; Prevotellaceae</strong></td>
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</tr>
<tr>
<td><em>Veillonella spp.</em></td>
<td>Lys, Orn</td>
<td>Lys (cadaverine, CO₂), Orn (putrescine)</td>
<td>Human, Pig</td>
<td>Rumen, stomach</td>
<td>20, 122, 152, 153</td>
</tr>
</tbody>
</table>
especially in the re-assimilation of ammonia derived from the breakdown of proteins and AA (23). However, in humans and mono-gastric animals, the proteins in gut bacteria mainly come from the assimilation of dietary and host-derived AA. Because the small intestine is the major site for nutrient digestion and absorption and because the absorption of AA is limited in the large intestine (6, 37), AA utilization by bacteria in the GI tract represents an important factor in AA homeostasis. Therefore, studies on the mechanism of AA biosynthesis are needed to improve the efficiency of utilization of dietary protein and AA.

AA composition varied among different bacteria strains (Table 2). In gram positive bacteria, alanine proportion was higher in *Staphylococcus aureus* cells. Proportions of arginine, proline and phenylalanine were higher in the cells of *Streptococcus* spp. (Table 2). Compared to gram positive bacteria, proportions of lysine and histidine were higher in cells of *Selenomonas ruminantium* and *Escherichia coli* strains. This result suggests that the “essential” AA for the growth of gut bacteria might be species specific. The conservation and variation in the AA composition of bacterial cell proteins in different bacterial species might partially reflect the evolutionary relationships of different organisms (38). Therefore, it is possible that certain AA could be utilized as biological markers to monitor the gut bacteria composition and activity especially for potential pathogens.

### 4.2. Biosynthesis of AA

As mentioned above, the AA incorporated into bacterial cells also derive from *de novo* synthesis using various substrates. Studies with pure bacteria cultures showed that ammonia might be the preferred nitrogen source and support the fastest growth for *Escherichia coli* (39). Ruminal bacteria, such as *Prevotella bryantii*, *Selenomonas ruminantium* and *Streptococcus bovis*, also synthesize various AA using ammonia as the sole nitrogen source in vitro (35, Table 2). However, the addition of peptides or AA mixtures decreased the *de novo* synthesis of AA in a dose dependent manner especially for proline and aromatic AA (phenylalanine and tyrosine) (35). It was estimated that, in ruminal bacteria, approximately 70% of the bacterial AA nitrogen was derived from ammonia in the presence of physiological concentrations of peptides (35). Similar observations were found for mixed bacteria which obtained 65% and 35% of their nitrogen from peptides and ammonia, respectively, when both were available (40, 41). It seems that the *de novo* synthesis of AA might be important for bacteria in the rumen.

Some investigators suggested that the biosynthesis of AA by bacteria in the digestive tract of mono-gastric animals may regulate AA homeostasis in the...
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host (5, 6, 42). When pigs were fed a diet containing $^{15}$NH$_4$Cl and [U-$^{14}$C]-polyglucose, the incorporation of $^{14}$C into essential AA and of $^{15}$N into lysine was detected (43). It was found that the small intestine was the major site for the absorption of microbial derived essential AA especially lysine even if the isotopic $^{15}$N enrichment of microbial lysine was higher in the large intestine (37). Similar observations were also obtained from the study with human subjects (44). Studies on the preferred nitrogen source for the bacterial de novo synthesis of lysine showed that the retention of $^{15}$N from $^{15}$NH$_4$Cl was higher than from $[^{15}N]$-urea (44, 45). The possibilities are a) the small-intestinal bacteria have a low activity of urease and thus unable to utilize urea efficiently (5); b) $[^{15}N]$-urea could be diluted by unlabeled urea from both systemic and local (enterocytes) metabolism of AA and ammonia (5, 46). Additionally, the AA required for the synthesis of bacterial protein might partially derive from the AA synthesized de novo (Table 2). Because extensive nitrogen recycling occurs in the gut (7), it would be important to determine the nitrogenous precursors for microbial AA synthesis, the proportion of the microbial AA to account for first-pass intestinal AA metabolism, the metabolic fate of AA in microbial proteins, and factors that regulate these processes (5, 42).

The contributions of the de novo synthesized microbial AA to the AA requirements of humans and mono-gastric animals are still uncertain (5, 6, 37, 42). Quantitative estimations showed that the de novo synthesized microbial lysine account for about 10% to 100% of the daily lysine requirement in pigs and the microbial lysine enrichment in the ileum account for 44% of lysine in the plasma of human subjects (43, 44). However, the above estimations ignored the net loss of AA during the first-pass intestinal AA metabolism (47). It is now known that there is substantial catabolism of AA by small-intestinal mucosal cells and small-intestinal bacteria (7, 21, 26, 48-50). Because nonruminants exhibit a negative nitrogen balance when fed an AA- or protein-free diet, bacteria do not make a significant contribution of AA to the host.

4.3. Catabolism of AA and production of important metabolites

Not all the AA ingested can be absorbed and enter the blood stream. As one of the metabolic fates, quantitatively significant amounts of dietary AA are catabolized by enterocytes during first-pass metabolism (7). Both in vitro and in vivo studies showed that pig small-intestinal mucosal cells degrade many non-essential AA, while the oxidation of essential AA by enterocytes is limited in vitro (47-50). Compared to enterocytes, AA catabolism in ruminal bacteria as well as microorganisms in the large intestine of humans and animals were extensive (51, Table 1). Theoretically, gut bacteria harbor the ability to catabolize almost all kinds of AA. However, AA such as glutamine/glutamate, asparagine/aspartate, lysine, serine, threonine, arginine, glycine, histidine and branched-chain AA might be the preferred substrates for degradation by gut bacteria (Table 1). The major pathways for microbial AA catabolism are deamination and decarboxylation. The fermentation products of AA include ammonia, short-chain and branched-chain fatty acids (e.g., acetate, propionate, butyrate, valerate, isobutyrate, and isovalerate), phenolic and indolic compounds (metabolites from phenylalanine and tryptophan), organic acids (lactate, formate, succinate, and oxaloacetate), gaseous compounds (mainly carbon dioxide, hydrogen, hydrogen sulfide and methane), and amines (e.g., agmatine, putrescine, spermidine, and spermine) (12, 51-53, Table 1). Gut bacteria such as clostridia could also obtain energy from AA catabolism through the Stickland reaction and the major metabolites are branched-chain fatty acids and ammonia (52, Table 1). In the gut, all of these microbial AA metabolites form a highly complex reservoir that has a potential impact on the physiology of the gut epithelium (12). Because the overall activity of bacteria in the small intestine is similar to that in the large intestine, it would be of great nutritional importance to determine whether AA catabolism in gut bacteria affects growth and health in the host.

Studies revealed that some of the metabolites from the AA catabolism by bacteria in the large intestine might be crucial for the physiopathology of the colon disease (12). Gaseous compounds (hydrogen sulfide and nitric oxide), nitrogenous products (e.g., ammonia, polyamines and nitrite), branched-chain fatty acids, as well as phenolic and indolic substances may serve as biomarkers for evaluating bacterial fermentation of dietary components and risks of colon cancer. The details of these AA metabolites and their impact on the physiopathology of the colon epithelium are summarized elsewhere (12). Substrates for the production of the detrimental AA metabolites by bacteria in the large intestine may be mainly derived from the small intestine. Therefore, it is important to define the factors and mechanisms that modulate nutrient flows and metabolic interactions in the small intestine as well as their impact on the physiology and micro-ecology of the large intestine (19).

4.4. Compartmental AA metabolism in gut bacteria

AA metabolism in the gut lumen might be compartment specific due to the differences in microbial community composition along the digestive tract (1, 14, 18, 20, 21, 24). For instance, proportions of arginine and proline were higher in the cells of small-intestinal bacteria and colonic bacteria when compared with ruminal bacteria (Table 2). However, proportions of serine and cysteine were higher in colonic bacteria than small-intestinal bacteria (Table 2). Furthermore, changes in the AA composition of the bacterial community might reflect the composition, abundance and activity of certain bacteria in specific gut segments.

Changes in the microbial ecology along the digestive tract will rather affect the compartment-wise AA metabolism in the lumen of intestine. Recent studies suggested that the bacterial AA utilization might mainly for the synthesis of bacterial protein in the small intestine while catabolism dominant the AA metabolism in the large intestine especially under low carbohydrate conditions (26, 21, 14). Meanwhile, it was found that in the pig small intestine, the utilization of AA by jejunal microbiota might be different from that of ileal microbiota in vitro (21). The
study also suggested that the utilization/metabolism of specific AA in small intestinal bacteria might be dependent on the cross-feeding of different bacterial species (21). As consequences, this might regulate the AA and nitrogen metabolism in the gut of the host in a multi-compartmental manner (62).

4.5. Metabolic interactions among gut bacteria and host

Early studies with germ free and conventionalized mice revealed that the gut microbiota altered the distributions of free AA in different regions of the GI tract (54). This finding led to an interesting and important hypothesis that the gut bacteria may play an important role in host AA homeostasis and health through multiple pathways. Such metabolic interactions exist among different bacterial species in the GI tract or between bacteria and the host at the local level (mucosal cells) and systemic level (whole body) and even within different compartments of the same intestinal section.

Metabolic interactions among gut bacteria may occur directly through the digestion of substrates (e.g. cross-feeding) and indirectly via selective pressure such as competition, selection and adaptation (9). As for the AA metabolism in gut bacteria, it is most likely that the ammonia produced from AA deamination could serve as a nitrogen source for the biosynthesis of bacterial AA when carbohydrates are available. Recent in vitro study showed that cross-feeding might exist in the catabolism of aromatic AA by colonic Bifidobacterium longum and Clostridium coccoides (55). After the depletion of glucose, the hydroxyphenylactic acid produced from the degradation of phenylalanine by B. longum could be further degraded by C. coccoides (55). In the large intestine, one bacterial species might also affect the nutrient metabolism of its “neighbors” indirectly. When germ-free mice were colonized with Eubacterium rectale and Bacteroides thetaiotaomicron (members belonging to the two dominant bacterial phyla present in the human distal gut microbiota), E. rectale adapted to the presence of B. thetaiotaomicron by reducing the production of its glycan-degrading enzymes, increasing expression of select AA and sugar transporters, and synthesizing glutamine/glutamate and D-alanine (56). However, the importance of the microbe-microbe interactions (e.g., feedback loops or molecular cross-talk) in intestinal AA metabolism is unknown.

Microbial metabolites may modulate gene expression in bacteria and their production of enzymes related to AA metabolism in the digestive tract. Compared to the laboratory medium, when the probiotic bacteria Lactobacillus plantarum pass through the GI tract of mice, expression of the genes involved in the acquisition and synthesis of AA increased dramatically (57). For instance, glutamate-5-semialdehyde dehydrogenase participates in the conversion of glutamate to proline and argininosuccinate synthase converts citrulline to arginine (57). Further studies showed that several genes (e.g. argininosuccinate synthase) displayed intestinal compartment-specific activity (small intestine > colon) (58). However, proteomic studies on the interactions between Lactobacillus fermentum and intestinal epithelium cells indicated that, compared to laboratory medium, L. fermentum reduced the production of proteins related to arginyl-tRNA synthetase (protein synthesis) and aspartate-semialdehyde dehydrogenase (glycine, serine and threonine metabolism and lysine biosynthesis) when exposed to the lumen of the rabbit jejunum (59). The contradictory results may be due to the physiological characteristics of different Lactobacillus species, different animal models or diets used. Recent work on the functionality of the human ileostomy effluent microbiota using the metatranscriptomics approach revealed that about 25% of the sequences retrieved from the mRNA enriched cDNA-amplified fragment length polymorphism profiles were related to metabolism and about 20% of these metabolism-related genes encoded proteins participating in transport and metabolism of AA (20). Examples include alanine dehydrogenase produced from bacteria belonging to the order of Bacteriodales, aspartate kinase from the order of Clostridiales, glutamate synthase and AA transporters from the order of Lactobacillales, and succinylglutamate desuccinylase from the order of Enterobacteriales (20). These results indicate that bacteria in the small intestine are active in the metabolism of nitrogenous compounds and have developed adaptive strategies to survive and propagate during the co-evolution with its host.

Increasing evidence indicates that the gut microbiota plays an important role in the physiology and metabolism of enterocytes, thereby regulating the nitrogen recycling within the gut and the whole body nitrogen metabolism. For example, during in vitro incubation with L. fermentum, Caco-2 cells increased the production of proteins that were beneficial for gut integrity, including voltage-dependent anion channel 1, glutathione transferase, and heat shock protein gp96 (59). Glutathione transferase family enzymes detoxify xenobiotics and, therefore, reduce the oxidative stress of cells (60). These enzymes can also remove toxic metabolites and may interact with ATP-binding cassette transporters (60, 61). These findings suggest that enterocytes could respond and adapt to the gut microbiota either by regulating the transport of nutrients or by transforming diet- or gut bacteria-derived substances to sustain mucosal integrity and function. Therefore, enterocytes likely develop strategies to maintain their protein balance by controlling nitrogen cycling within the gut, while benefiting its bacterial ecosystem. The anabolism and catabolism of AA by both enterocytes and perhaps gut bacteria limit the availability of dietary AA to extraintestinal tissues (44, 47). Meanwhile, nitrogenous substances (e.g., digestive enzymes, bile, mucins, cell debris and urea) secreted into the gut lumen are subjected to digestion or fermentation in the small intestine and the large intestine (5, 7). It is likely that gut bacteria utilize the ammonia generated from the catabolism of extracellular and intracellular proteins, AA, or urea for the synthesis of bacterial protein (5, 6, 7, 37, 43, 44). This could be regarded as a form of nitrogen recycling, which is of nutritional importance especially for animals fed a low-protein diet. Although the absorption of AA is limited in the large intestine (44), AA synthesized in this segment of the gut may provide AA to luminal bacteria (7, 62).
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At the whole-body level, the modulation of host metabolism by gut microbiota may occur in multiple tissues and cell types (Figure 1). Studies aimed at comparing the multi-compartmental metabolic profiles of conventional mice and its germ-free counterparts showed that, in the presence of gut microbiota, concentrations of creatinine in urine, of hypotaurine in the liver, of alanine and creatine in the small intestine were substantially reduced (62). However, the presence of the gut microbiota resulted in increased levels of oxidized glutathione in the liver, of tyrosine, glutamate, alanine and aspartate in the small intestine, and of creatine, glutamine, and aspartate in the colon (62). It is well known that creatinine and creatine are closely related to muscle mass and arginine metabolism (63). Also, glutamine/glutamate, aspartate, and glutathione play important role in the regulation of nitrogen and energy balance in tissues and at the whole body, including the fluxes of the citric acid cycle and the urea cycle, as well as protein synthesis and degradation (2, 3, 48, 62, 64, 65). Therefore, it could be concluded that nitrogen and AA metabolism in the gut microbiota and the underlying metabolic interactions with the host may be important in the regulation of host protein and energy balance. Based on marked differences in intestinal microbial AA metabolism among subjects, the concept of personalized requirements of dietary proteins should not be neglected (8). However, the linkage between the multi-compartmental metabolic profiles and host health/disease is still not clear. The development of certain biomarkers and databases will help to better understand, predict, prevent and treat life-threatening metabolic diseases.

5. FUNCTIONAL ASPECTS OF AA METABOLISM IN GUT BACTERIA

Apart from the nutritional importance of nitrogenous substances to the growth of gut bacteria, AA metabolism in gut bacteria may serve as an important “survival strategy” for the bacteria to adapt and survive in the gut and also “cross-talk” to their neighboring species and eukaryotic host. Therefore, it is important to define the role of AA metabolism in the survival of gut bacteria as well as the impact to their surrounding environments and the consequences on host health and disease.

5.1. Adaptation and survival

Gut bacteria have many mechanisms to cope with harsh, variable, rapidly changing environment of the digestive tract. Stresses, such as low pH, nutrient limitation, and starvation, are now taken into consideration (66). It was found that bacteria in the dental plaque ecosystems maintained the neutral pH of their environment (acid-neutralizing activity) by the catabolism of different AA thus showed a beneficial effect to the prevention of caries. For instance, in *Fusobacterium nucleatum*, rates of glutamate and aspartate fermentation as well as ammonia production were higher at pH 5.0 than at pH 5.5 (67). In *Streptococcus gordonii*, the expression of arginine deiminase was induced by low pH, which resulted in elevated production of ammonia (68). These findings can aid in development of new strategies to prevent caries and improve oral health (67, 68).

In the GI tract, a low pH can be induced by either hydrochloric acid secreted from the stomach epithelium or short chain fatty acids (formerly known as volatile fatty acids, VFA) from the bacterial fermentation of carbohydrates. This may result in acid stress in gut bacteria, therefore affecting the survival of gut bacteria, and determining the survival of potential pathogenic bacteria. Early studies demonstrated that the decarboxylation of gamma-aminobutyric acid (GABA) and putrescine by *Bacteroides fragilis* was optimal under acidic conditions (pH 6.0) (69). When the pH of the medium was changed from 7.0 to 6.0, the preferred AA for decarboxylation in *Clostridium perfringens* shifted from arginine and GABA to lysine and putrescine (69). In *Escherichia coli*, two acid resistance systems have been discovered namely the acid resistance system 2 and 3 (AR2 and AR3), depending on the catabolism of AA (70). The AR2 and AR3 require extracellular glutamate and arginine, respectively. However, both AA can be decarboxylated to alter the membrane potential from a net inside negative to a net inside positive charge, leading to an increase in internal pH (ΔpH) (70).

The intestinal metabolism of AA may also be important for the survival of gut bacteria under conditions of nutrient limitation and starvation during gut transition. When oxygen is limiting, the production of aspartase increased in *Campylobacter jejuni* (71). As a consequence, the conversion of aspartate to fumarate and ammonia was augmented with subsequent increases in fumarate utilization and bacterial growth (71). In *C. jejuni*, aspartase is one of the key substances in the metabolic pathway that controls the utilization (including catabolism) of AA and ATP production. Therefore, aspartase is critical for the survival of *C. jejuni* in the lumen of the small intestine under anaerobic conditions (71). In the large intestine, low levels of luminal nutrients can trigger starvation and death of bacteria especially in the presence of high concentrations of organic acids. It was shown that *Escherichia coli* increased its lysine decarboxylation activity under phosphate-deficient conditions (72). These findings suggest that, in response to nutrient restriction and acid stress, gut bacteria develop multiple strategies to survive in the intestine by modulating their AA metabolic pathways.

5.2. Production of important molecules

Studies over the last decades have shown that gut bacteria respond to their environments and affect the physiology and metabolism of their neighboring species and eukaryotic host through the synthesis of a wide variety of AA and their metabolites. It is generally regarded that the peptidoglycan produced from gram positive bacteria and lipopolysaccharide generated from gram negative bacteria plus some bacteria-derived macromolecules (e.g., glycan ligands) mediate signaling pathways in gut epithelial cells and regulate the host immune function (73-75). Additionally, it has been reported that the Rgg proteins produced by the pathogenic *Streptococcus pyogenes* strain regulate the synthesis and metabolism of virulence factors in the bacteria and the effects are associated with the
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**Figure 1.** Schematic diagram of the multi-compartmental metabolism of amino acids in the gut and extraintestinal tissues of mono-gastric animals. AA, amino acids; AHLs, acyl homoserine lactones; AI-2, autoinducer-2; Ala, alanine; BCAA, branched chain amino acid; BCFA, branched-chain fatty acids; BCKA, branched-chain ketoacid; CO₂, carbon dioxide; GSH, glutathione; GSSG, glutathione disulfide; Glu, glutamate; Gln, glutamine; Glu / Gln Cycle, Glutamate / Glutamine Cycle; Gly, glycine; H₂S, hydrogen sulfide; alpha-KG, alpha-ketoglutarate; LPS, lipopolysaccharides; Lys, lysine; Met, methionine; NDC, non-digestible carbohydrates; NH₃, ammonia; PG, peptidoglycan; Pyr, pyrovate; SCFA, short chain fatty acids; SLP, S-layer protein; TCA Cycle, Tricarboxylic Acid Cycle.

Catabolism of arginine and serine (76). In *Streptococcus bovis* HC5, the production of a broad-spectrum antibiotic bovicin HC5 inhibited the growth of pure cultures of hyperammonia-producing bacteria as well as AA degradation and ammonia production by mixed ruminal bacteria (77).

Recent findings have indicated that some small molecules produced by gut bacteria play crucial role in quorum sensing and biological processes, such as biofilm formation and expression of virulence factors (78). Among these, the acyl homoserine lactones (AHLs) and autoinducer-2 (AI-2) are derived from S-adenosyl methionine, an important metabolite of methionine (79). It is now known that AI-2 is essential for the adherence to HeLa cells, mobility, and expression of virulence genes in enteropathogenic *E. coli* (80). In addition, formation of AI-
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2 affects the attachment of *L. acidophilus* to Caco-2 cells *in vitro* (81). The production of AI-2 in *Streptococcus suis* is stimulated in the addition of 0.5% sodium chloride or glucose (82). Furthermore, *E. coli* interact with neighboring species by adjusting the production and consumption of AI-2 (83). Because AI-2 is produced and recognized both by gram-positive and gram-negative bacteria, pro- and anti-AI-2 interactions among gut bacteria and their association with the eukaryotic host within the digestive tract can affect the microbial community composition and host health (78).

Current data suggest that AHL molecules mediate the interactions between gut bacteria and the host. Also, N-3-oxododecanoyl homoserine lactone produced by *Pseudomonas aeruginosa* accelerates apoptosis in macrophages and neutrophils, while possessing an immunomodulatory effect on human peripheral blood mononuclear cells (84, 85). Conversely, as one of defense mechanisms, host cells can inactivate (via degradation) the AHL molecules produced by *P. aeruginosa* *in vitro* (86). Although it is not clear whether similar AHLs-mediated interactions occur within the digestive tract, the above findings raise important questions about the physiological significance of the microbial metabolites of methionine and related AA. Namely, can these metabolites serve as potential biomarkers for monitoring the microbe-microbe interactions? Metabolic profiles of quorum-sensing signals and related molecules will aid in the development of diagnostic and therapeutic tools for the well-beings of both humans and animals (87).

Polycationic nitrogenous substances (e.g., polyamines) are important products of AA metabolism in luminal microbes of the small intestine. Ornithine, which is derived from arginine, proline, glutamate, and glutamine, is decarboxylated by ornithine decarboxylase to produce putrescine. Putrescine is also formed from arginine sequentially via arginine decarboxylase (to yield agmatine) and decarboxylation of agmatine by agmatinase (to generate putrescine). Putrescine is converted into spermidine and spermine via spermidine synthase and spermine synthase, respectively. Polyamines have long been recognized to important roles in cell physiology. For example, polyamines act as antioxidants to protect cells from oxidative damage. As positively charged compounds, polyamines participate in many cellular processes through binding with RNA, DNA, nucleotide triphosphate, proteins, and other negatively charged molecules. Through these interactions, polyamines regulate gene expression, signal transduction, ion channel function, DNA and protein synthesis, and apoptosis. Thus, polyamines are essential for proliferation, differentiation, and function of bacteria and enterocytes. When cells are stimulated with growth factors, one of the first crucial events is the induction of polyamine synthesis, which precedes increases in DNA replication and protein synthesis. Thus, an increase in polyamine levels is associated with enhanced growth of intestinal mucosal cells and microorganisms. Conversely, depletion of cellular polyamines arrests cell growth.

6. DIETARY MODULATIONS OF AA METABOLISM IN GUT BACTERIA

Bacteria thriving in the digestive tract mainly rely on the utilization of substances of food origin. Therefore, diets have profound influence on bacterial metabolism, and specific dietary components may have selective effects on the population and metabolism of the microbiota. Over the last decades, there has been interest in effects of some dietary factors, such as protein, nondigestible carbohydrates, probiotics, synbiotics or phytochemicals on gut bacteria and host health (Figure 1). These results are highlighted in the following sections.

6.1. High protein diet

In the small intestine of mono-gastric animals, the daily requirement of AA for the first-pass metabolism and absorption of AA are constant under normal conditions. When AA are supplemented to the diet, the entry of AA into the portal vein increases (88). However, adaptive metabolism of the small intestine may occur in response to dietary protein intake. When high protein intake exceeds the capacity of digestive enzymes and AA transporters, some of protein and AA in the diet would enter the large intestine. To date, data on the regulation of AA metabolism in the small intestine and its luminal bacteria is limited. Also, little is known about high protein diet on the hindgut ecology (19).

Research showed that approximately 3-12 grams of dietary protein and peptides entered the human large intestine every day and served as nitrogen sources for the gut microbiota (14, 89). High levels of proteins and peptides in the large intestine could lead to an increased production of ammonia due to the actions of proteases, peptidases, deaminases, and deiminase produced by gut bacteria (23, 90, 91). When subjects are fed a high-protein diet, levels of sulfide and branched-chain fatty acids are elevated due to the bacterial fermentation of sulfur-containing AA and branched-chain AA (92, 93), but butyrate concentrations and numbers of butyrate-producing bacteria are decreased in the large intestine as well in the feces (94). It is widely regarded that butyrate is the main energy source for colonic epithelial cell, thus, a decrease in butyrate concentration and an increase in concentrations of ammonia and sulfide may explain the detrimental effect of high protein diet on the large intestine (e.g., increased incidence of colon cancer).

The structure and AA composition of proteins can affect their hydrolysis in the GI tract and nitrogen metabolism in gut bacteria. Results of *in vitro* study indicate that compared with casein, sulfate production from the bacterial fermentation of bovine serum albumin is higher and that dietary protein from the meat is an important substrate for sulfide generation (93). In addition, AA, such as tryptophan, proline, tyrosine, and isoleucine, strongly inhibit the protease activity of *Clostridium sporogenes* (90). In *Selenomonas ruminantium*, the urease activity is higher when serine or threonine is used as a substrate. However, urease activity decreases markedly when histidine is added to medium (95). These findings
suggest that proteins, peptides or AA in the large intestine not only affect the production of toxic substances, but also regulate the bacterial fermentation, AA degradation, and nitrogen recycling. Furthermore, the active metabolism of nitrogenous substances by bacteria in the digestive tract, especially in the large intestine, is also influenced by the availability and structure of carbohydrates (4, 89).

6.2. Non-digestible carbohydrates and availability of carbon source

Non-digestible carbohydrates (NDC) or dietary fibers are normal constituents of most foods derived from plants. They escape digestion in the small intestine as the host lacks the necessary degrading enzymes and pass into the large intestine. NDC include polysaccharides such as resistant starch, pectin, inulin, guar gum, wheat bran, cellulose, lignin, and oligosaccharides (89). According to the definition, prebiotics belong to the category of NDC and selectively stimulate the growth of potentially beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* (89, 96). NDC affect the AA metabolism in gut bacteria either by regulating the bacterial composition and abundance or by providing the carbon source for the growth of microorganisms. In the three-stage continuous culture, the addition of inulin and galacto-oligosaccharides increased the numbers of lactobacilli in the proximal colon, together with a small increase in bifidobacteria, peptostreptococci, enterococci and *Clostridium perfringens* (97). The two carbohydrates stimulated the synthesis of nitroreductase and azoreductase (97). At neutral pH, the addition of starch to the media significantly decreased the bacterial production of amines, phenolic and indolic compounds, and branched-chain fatty acids both by pure and mixed bacteria cultures (14, 53, 69, 98). Similarly, the reduced production of phenolic and indolic compounds was reported for oligofructose added to the pure cultures of *Bifidobacterium* and *Bacteroides* (55). Recent studies on the effect of prebiotics on AA metabolism at the whole-body level revealed that galacto-oligosaccharides increased the urinary excretion of carnitine and taurine as well as fecal excretion of glycine in human infants, while the addition of prebiotics decreased the urinary excretion of lysine and alpha-keto-isocaprate (99). The findings indicate that NDC affect AA metabolism within the digestive tract and at the whole-body level. However, the underlying mechanism and effects on are not clear. Nonetheless, many gut bacteria such as bacteroides, bifidobacteria, ruminococci, eubacteria and clostridia can degrade polysaccharides and produce simple sugars (100). As one possible mechanism explaining the beneficial effect of NDC, the simple sugars produced could be used by the bacteria or shared with other bacteria species and affect their AA metabolism. Interestingly, in the presence of glucose, significant reduction in protease production by *Clostridium sporogenes* was observed (90). The production of phenolic and indolic compounds from aromatic AA also decreased in mixed bacteria in response to the addition of glucose (101).

The highly stimulated fermentation and growth of bacteria in the proximal colon by NDC resulted in the formation of short-chain fatty acids and thus a decrease in luminal pH (89, 97, 102). As one of the important parameters of the gut environment, the decreased luminal pH can affect microbial metabolism and composition in the large intestine (10, 25). Consistent with data on carbohydrate availability, the microbial production of amines, branched-chain fatty acids, phenolic and indolic compounds from AA decreased at pH 5.5 compared with neutral pH (14, 53, 101). However, the above conclusions are based on *in vitro* studies. In the large intestine, apart from the short-chain fatty acids, the shifts of individual fatty acids also affect the luminal pH. Therefore, it seems essential to determine the role of individual fatty acids on the growth, community composition and AA metabolism of gut bacteria both *in vitro* and *in vivo* (25). Meanwhile, little is known about the substrate preferences of the majority of gut bacteria (10). Therefore, caution must be taken when prebiotics are introduced into the gut, because they may stimulate one or more elements of the microbiota in addition to the target groups whose activation may trigger a series of unfavorable biochemical reactions and serious health problems (10). Furthermore, factors such as nature of the substrate, dietary components, gut environment, microbial composition and metabolic cross-feedings might be important when evaluating and assessing the mechanism of the beneficial effect of NDC or dietary component (10, 103).

6.3 Probiotics and symbiotics

Probiotics are microbial food supplements that beneficially affect the host by improving its intestinal microbial balance, while symbiotics are the combination of prebiotics and probiotics (96). Meanwhile, many bacteriocin-producing species belong to the category of probiotics. Increasing evidence shows that probiotics and symbiotics are beneficial to the health of humans and animals by improving the nitrogen metabolism within the gut and at the whole-body level (7). Here, we provide an update on the progress of research regarding the regulatory role of probiotics and symbiotics on host AA metabolism.

Recent findings indicate probiotics or symbiotics modulate the AA metabolism in animal models and humans in a multi-compartmental mode. Compared to germ-free mice, the introduction of *Lactobacillus paracasei* to the intestine of germ free mice reduced concentrations of serine and glutamine in the duodenum and concentrations of glutamate, glutamine, glutathione, methionine, alanine, glycine, cysteine and creatine in the jejunum and ileum (104). Also, in response to the supplementation with *L. paracasei* or *Lactobacillus rhamnosus*, hepatic concentrations of leucine and isoleucine, as well as concentrations of citrulline, lysine and creatine in urine were decreased (105). On contrary, concentrations of glutamate, glutamine, lysine and glucose increased in plasma and the fecal excretion of lysine and glucose increased (105). In another study, the authors found that supplementing *L. rhamnosus* or *L. rhamnosus* plus galactooligosaccharides to human baby microbiota mice resulted in increased concentrations of alpha-keto-isovalerate and creatine in urine (99). Both probiotics and symbiotics enhanced fecal excretion of glutamate, glutamine, branched-chain AA, alanine, and glycine. Compared with
the probiotic L. rhamnosus, dietary supplementation with galacto-oligosaccharides reduced the fecal excretion of aspartate, asparagine, lysine, methionine and aromatic AA (99). The supplementation with both probiotics and synbiotics reduced hepatic concentrations of alanine in the liver (99). The dietary supplementation of a synbiotic food containing Lactobacillus acidophilus, Bifidobacterium longum and fructooligosaccharides reduced the fecal excretion of tyrosine, phenylalanine, alanine, glutamate, lysine, glycine, valine and isoleucine in humans (106). These differential results may result from variations in the metabolic characteristics of humans and mice, probiotics and prebiotics used, etc. However, all the findings point to a role for probiotics and synbiotics in regulating AA metabolism in intestinal microbes. Collectively, the results provide us with a broader view of effects of probiotics and synbiotics on health. Further studies are essential to uncover the underlying mechanisms and the potential biological significance.

6.4. Phytochemicals
Phytochemicals are bioactive non-nutrient plant compounds present in fruits, vegetables, grains, and other plant foods. Ingestion of these substances by humans and animals has been linked to reductions in risk of major chronic diseases (107). A number of studies over the last decades showed that phytochemicals might affect the growth and metabolism of proteolytic and AA-fermenting rumen bacteria. For example, work with pure cultures of ruminal bacteria revealed that saponin from Yuca schidigera inhibited the growth of Ruminobacter amylophilus, Butyribivio fibrisolvens, Prevotella bryantii, and Streptococcus bovis and with a modest decrease in ammonia production (108, 109). It was demonstrated that condensed tannin from Lotus corniculatus inhibited the growth of Clostridium proteoclasticum, B. fibrisolvens, Eubacterium spp. Ruminococcus albus, Fibrobacter succinogenes and S. bovis, and rates of proteolysis in vitro (110). In addition, the growth of proteolytic bacteria such as B. fibrisolvens, R. amylophilus and S. bovis was reduced by saffron (Crocothyrsis vicifolia) condensed tannin (111). The inhibitory effect of tannin to bacteria was due to the ability of tannins to form complexes with the cell envelop of bacteria, leading to morphological changes of the cell wall and the extracellular enzymes secreted (111, 112). Also, essential oil inhibited the growth of most pure bacteria tested, with S. bovis being the most resistant species, and P. ruminicola, Clostridium sticklandii, and Peptostreptococcus anaerobius the most sensitive species (113). The mode of action of essential oil on the formation of ammonia involves reduction in deamination of AA by hyper-ammonia-producing bacteria (114).

Plant phenolic compounds from tea and berries have also been reported to have antimicrobial properties and modulate gut microbiota in humans. Studies with pure bacteria cultures isolated from human fecal samples demonstrated that the growth of certain pathogenic AA-fermenting bacteria such as Clostridium perfringens, Clostridium difficile, Streptococcus pneumoniae, Bacteroides fragilis, Staphylococcus aureus, Salmonella typhimurium and Escherichia coli was significantly repressed by tea phenolics and their derivatives, while commensal anaerobes like Lactobacillus rhamnosus, Bifidobacterium spp. and Clostridium sp. were less severely affected (115). It was also found that caffeic acid generally exerted a more significant inhibitory effect on the growth of pathogens (e.g., B. fragilis and C. difficile) than epicatechin, catechin, gallic acid and 3-O-methylgallic acid (115). These results suggest that the chemical structure of a phytochemical might be important for its antimicrobial effect (115). The anthocyanins from berries were also effective in inhibiting the growth of pathogenic Staphylococcus spp., Salmonella spp. Bacillus cereus and Helicobacter pylori (116, 117). The anti-growth effect of berry phenolics on Helicobacter pylori may be mediated through urease inhibition and disruption of ATP production from proline due to an inhibition of proline dehydrogenase (118). Thus, modulation of the gut microbial ecology may be one of the mechanisms for phytochemicals such as polyphenol, tannin, saponin and essential oil to promote the health status of humans and animals (119). However, further in vitro and in vivo studies are warranted to define the effects of these phytochemicals on microbial nitrogen metabolism and microbial community structure in relation to differences in diets and gut environments. Other issues to be considered should include chemical structure, antimicrobial properties of phytochemicals, long-term effects, the interplay between phytochemicals and gut microbiome, and the consequence to host health (114, 119, 120).

7. CONCLUSIONS AND PERSPECTIVES
During the evolution of animals and their gut microbiota, dietary AA may serve as one of the selective forces that shape the diversity of the AA-fermenting bacteria and their metabolic pathways for AA utilization in the digestive tract. Through the metabolism of AA, gut bacteria survive, thrive and compete with each other in the complex dietary context and gut environment. The AA-derived molecules produced by gut bacteria create new niches for the well-beings of the bacteria but also present new pressure for the surrounding prokaryotic species and eukaryotic host. Ultimately, gut bacteria affect host health by modulating host nutritional status and metabolic processes in response to consumption of different diets. To date, little is known about the genetics and physiology of the gut microorganisms, which limits our understanding of the functional aspects of the microbiome (the whole microbial community) (9). At present, little is known about utilization of nitrogenous substances (e.g., plant proteins, animal proteins, peptides, free amino acids, and ammonia) by small-intestinal bacteria in nonruminants (e.g., pigs and chicken). Fortunately, with the development of new sequencing techniques and new metabolite analysis platforms, our appreciation of the holistic biological processes in the gut and the whole body is expanding rapidly. Finally, the integration of metagenomics and metabolomics (11), as well as the development of systems biology, will surely help us better understand the mechanism of the in vivo interplays among dietary AA, gut microbiome and host under different nutritional and health conditions (8). Collectively, this work will lead to
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development of new concepts and methods for the formulation and management of foods and drugs to improve the well beings of humans, animals, and environment.

8. ACKNOWLEDGEMENTS

This work was supported by the Natural Science Foundation of China (30810103909), the National Basic Research Program of China (2004CB117500-4), the Texas AgriLife Research Hatch Project (H-8200), and the Thousand-People-Talent program at China Agricultural University. ZL Dai thanks the Chinese Scholarship Council for support of his study at Texas A&M University between February 17, 2009 and February 28, 2010.

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**Abbreviations:** AA, amino acids; AHB, acyl-homoserine lactones; AI-2, autoinducer-2; AR2 and AR3, acid resistance system 2 and 3; GABA, gamma-aminobutyric acid; GI tract, gastrointestinal tract; NDC, non-digestible carbohydrates
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**Key Words:** Gut Bacteria, Amino Acid Metabolism, Diversity, Modulation, Health, Review

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