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Gut microbiota role in dietary protein metabolism and health-related outcomes: The two sides of the coin

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ABSTRACT

Background: Human gut bacteria can synthesize proteinogenic amino acids and produce a range of metabolites via protein fermentation, some known to exert beneficial or harmful physiological effects on the host. However, the effects of the type and amount of dietary protein consumed on these metabolic processes, as well as the effects of the microbiota-derived amino acids and related metabolites on the host health are still predominantly unknown.
Scope and approach: This review provides an up-to-date description of the dominant pathways/genes involved in amino acid metabolism in gut bacteria, and provides an inventory of metabolic intermediates derived from bacterial protein fermentation that may affect human health. Advances in understanding bacterial protein fermentation pathways and metabolites generated at a global level via the implementation of 'omics' technologies are reviewed. Finally, the impact of dietary protein intake and high-protein diets on human health is discussed.
Key findings and conclusions: The intestinal microbiota is able to synthesize amino acids, but the net result of amino acid production and utilization, according to dietary patterns still needs to be determined. The amount of ingested dietary protein appears to modify both the diversity and composition of the intestinal microbiota as well as the luminal environment of the intestinal epithelium and peripheral tissues. The understanding of the consequences of such changes on the host physiology and pathophysiology is still in an early stage but major progress is expected in the near future with the investigation of host-microbe omics profiles from well-controlled human intervention studies.

1. Introduction

The dietary protein consumption level in humans is vastly different according to food availability and cultural dietary habits (Wu et al., 2014). Although insufficient protein consumption remains a persistent problem in the developing world, the average daily protein intake in countries from Western Europe and the United States of America is generally higher than the recommended dietary intake of 0.83 g protein kg^{-1} day^{-1} for adults (EFSA Panel on Dietetic Products, 2012; Rand, Pellett, & Young, 2003). In individuals consuming a high-protein (HP) diet as a way to reduce their body weight, the protein consumption generally consists of approximately two to three times the recommended dietary intake; and can even represent five times this latter value (Pesta & Samuel, 2014). Such diets have been shown to increase satiety, modify lipid metabolism, and facilitate short- and medium-term weight reduction (Westerterp-Plantenga, Nieuwenhuizen, Tome, Soenen, & Westerterp, 2009). Although a reduction of body weight in overweight and obese individuals is obviously associated with favorable outcomes in terms of health, such dietary modification are also associated with potentially deleterious effects in both healthy situations in the long-term and in some pathological situations, notably in kidney diseases (Juraschek, Appel, Anderson, & Miller, 2013) and in inflammatory bowel diseases (Jowett et al., 2004).

Besides host physiological factors, recent evidence demonstrates that human gut microbiota in the small and large intestine also plays a role in host dietary protein metabolism. The interplay

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between host and gut microbial metabolism is complex, with microbes utilizing and even competing for dietary and endogenous proteins. Fermentation of amino acids by gut bacteria produces metabolites that can affect host protein/amino acid uptake (transport) and metabolism, as well as affect host cell physiology (Davila et al., 2013). Bacteria can also synthesize amino acids, which can be provided to the host (Metges, 2000). However, the net result of amino acid synthesis and degradation remains largely to be determined along with the role of the gut microbiota for the management of whole body nitrogen metabolism (Neis, Dejong, & Rensen, 2015). Such knowledge is important since it will yield information regarding the role of the microbiota in the utilization of amino acids from dietary origin in different physiological and pathological situations, as well as the role of the microbiota in the production of metabolites that could be available for the host and impact host metabolism and other physiological functions.

Despite the relatively rapid transit of the luminal content in the small intestine, part of the amino acid pool released from proteins through the action of pancreatic enzymes can be used by the host enterocytes (Davila et al., 2013) as well as by the small intestinal microbiota (Dai, Zhang, Wu, & Zhu, 2010). Protein digestion in the mammalian digestive tract is a very efficient process, being generally equal to or even higher than 90% (Bos et al., 2005). In the large intestine, where the microbiota concentration is much higher and the transit time is longer than in the small intestine, the remaining protein is broken down to peptides and amino acids via extracellular bacterial proteases and peptidases (Macfarlane, Cummings, & Allison, 1986). In contrast to the small intestine, however, the amino acids generated cannot be absorbed to any significant extent by the large intestine epithelium, except during the neonatal period in mammals (Darragh, Cranwell, & Moughan, 1994). Gut bacterial fermentation of amino acids thus results in an accumulation of various metabolic end-products in the luminal content, some of these metabolites being largely absorbed through the large intestinal epithelial cells, while others are released in feces in large amounts (Davila et al., 2013). Several bacterial metabolites have also been shown to be active on colonic epithelial cells, which, as detailed below, depending on their luminal concentrations, can exert beneficial or deleterious effects.

Bacterial metabolites which are not fully metabolized/detoxified by the colonic epithelial cells during their transcellular journey from the intestinal lumen to the bloodstream may reach the liver through the portal vein and then peripheral tissues where they can exert some biological effects, notably on kidney functions.

Investigations into the effects of microbially-derived metabolites on human health and the interaction of the microbiota with the human host have previously been limited due to the complexity of interactions between these two systems. The rapid advance of 'omics' technologies are beginning to expand our understanding of the relationships between the human host and gut microbiota by allowing a global analysis of the flow of host- and microbially-produced metabolites and genes involved in specific biochemical pathways (Qin et al., 2010; Sridharan et al., 2014). A thorough characterization and understanding of the bacterial pathways involved in amino acid metabolism and their derivatives is required for precise interpretation and prediction of dietary protein effects on the host health. Currently, a comprehensive review of those bacterial genes and metabolic routes is lacking.

This review merges up-to-date genomic information regarding amino acid-related metabolism in gut bacteria with their potential effects on human health. A description of the dominant pathways for bacterial amino acid biosynthesis as well as for amino acid degradation into metabolites that may play different roles in human health is provided. Moreover, information on the enzymes and homologous genes involved in these pathways as deduced from the KEGG database (Kanehisa et al., 2014) is given. We then discuss the recent advances in understanding the effects of different dietary strategies (i.e. high-fat diet and HP diet) on the human gut microbiome and its role in protein/amino acid metabolism based on metagenomic and metabolomic studies. Finally, we analyzed how this metabolic activity, notably in terms of bacterial metabolite production, may be responsible for the effects of dietary protein intake levels on health-related outcomes in both physiological and pathological situations as well as underline research areas that need new developments.

2. Bacterial synthesis of amino acids

The effects of *de novo* production of amino acids by microbes on whole-body fluxes and human health are still not clearly understood. Bacterial production of amino acids that are accessible to the host may be useful to compensate indispensable amino acid deficiency in low quality protein diets. However, bacterially-produced amino acids could also have detrimental consequences in conditions such as insulin resistance in type 2 diabetes where systemic concentrations of amino acids such as aromatic and branched-chain amino acids are elevated (Neis et al., 2015). A deeper understanding of the effects of microbially-produced amino acids on host health is warranted, as well as a revision of the biosynthetic pathways of amino acids in bacteria which is provided here.

2.1. Pathways/genes involved in de novo biosynthesis of amino acids

Due to the high metabolic cost of synthesizing amino acids, the carbon backbone of all amino acids originates from common metabolic intermediates involved in processes such as the tricarboxylic acid cycle, the pentose phosphate pathway and glycolysis (Berg, Tymoczko, & Stryer, 2002). Among these intermediates, α-ketoglutarate plays a central role in amino acid biosynthesis through its conversion to glutamate, as well as its participation in the biosynthetic pathways of other amino acids. Amino acids can be grouped into families according to common starting products or use of common enzymes for synthesis. These consist of the following families: glutamate, serine, aspartate, pyruvate, and aromatic amino acid families, as well as several unique pathways for individual amino acids (Umbarger, 1978). It is important to note that an overwhelming amount of the literature on bacterial metabolism has historically been focused on a few bacterial taxa, namely *Escherichia coli* and *Salmonella typhimurium*, and to a lesser extent *Bacillus subtilis* and recently *Corynebacterium glutamicum*, thus creating a potential bias towards mechanisms found in these organisms. Although many of these pathways are conserved across bacterial lineages including those inhabiting the intestine, diversity is found among different bacterial species at both the species and strain level. For example, whole genome analysis has revealed that the common gut bacterium *Clostridium perfringens* lacks numerous amino acid biosynthetic genes for glutamate, arginine, histidine, lysine, methionine, serine, threonine, aromatic and branched-chain amino acids (Shimizu et al., 2002), while other *Clostridium* spp., such as *Clostridium acetobutylicum,* has a complete set of genes for amino acid biosynthesis (Nolling et al., 2001). The gut bacterium *Lactobacillus johnsonii* also appears incapable of carrying out *de novo* biosynthesis of almost all amino acids due to a lack of complete biosynthetic pathways, and exhibits an apparent dependence on exogenous host amino acids/peptides for protein synthesis (Pridmore et al., 2004). Other animal and human intestinal bacteria, including *Campylobacter jejuni*, *Helicobacter pylori*, *Enterococcus faecalis* and *Streptococcus agalactiae* have also lost certain amino acid biosynthetic pathways (Yu, Walker, Liu, & Zhang, 2009),