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Beyond traditional roles for amino acids

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Since the original discovery by Osborne and Mendel in 1914 about the need for certain amino acids for growth in rats, and the seminal work done by Rose to characterize the indispensable/dispensable amino acids in humans (1), the field of amino acid research has continued to evolve. The traditional focus of research in this field has been on aspects of deficiency, impacts on growth, and the nutritional supply of the minimum amount to ensure proper growth or maintain body protein mass. It is understandable why that has been the case, since mammalian protein, which is primarily made up of 20 α -amino acids, is an essential component of new tissues during stages of growth, and maintenance of tissues during stages of adulthood.

Individual amino acids have since been shown to play key roles in the human body beyond protein synthesis, most often in 'secondary' pathways, which are quantitatively of less importance, but can be of high functional importance. Some examples include: aspartate and glutamate for nucleic acid synthesis necessary for cell division, cysteine, glutamate and glycine for glutathione synthesis which is central for redox status, tyrosine for catecholamine synthesis involved in glycogenolysis and lipolysis, methionine in one-carbon metabolism to provide methyl groups for DNA methylation, and arginine for the synthesis of nitric oxide, to name a few (2). From a cellular point of view the 20 α -amino acids are all necessary for protein synthesis. There is also a tissue/cell type need for certain amino acids to form compounds necessary to perform a specific function as described above. To ensure that the body has access to amino acids to form new proteins, and/or form other metabolites, protein metabolism is constantly in a state of turnover – protein synthesis and breakdown. Thus, amino acids are also in a state of flux and free amino acids are available in a conceptual 'amino acid pool'. In humans this is most easily assessed by measuring plasma concentrations, although they are only a reflection of the cellular availability of amino acids within a compartmented metabolism.

Plasma amino acid concentration changes has been a major focus of interest, particularly in disease, since alterations from a 'normal' range could be suggestive of dysfunction. It has been suggested that obese individuals have lower concentrations of glycine, which appears to be associated with insulin resistance, and increased risk for type 2 Diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD) (3). Conversely, lower glycine concentrations are

associated with higher concentrations of branched-chain amino acids (BCAA, which include leucine, isoleucine and valine), which have been associated with obesity and increased risk of insulin resistance. Altered BCAA concentrations in obese humans are not a new observation and was first reported in 1969 by Felig et al. (4). There is now growing evidence that a high BCAA intake, which could explain in part a high BCAA concentrations, may be detrimental to metabolic health, possibly with different effects of isoleucine, valine and leucine (5). Interestingly, as reviewed by Gueugneau et al. (6), lower plasma BCAA concentrations are part of the metabolomic signature of plant protein intake, and this association may be part of the mechanisms that explains the favorable effect of plant protein sources in the diet. It remains difficult to decipher if this metabolic signature, driven by some amino acids such as BCAA, should be ascribed to the amino acids of plant/animal proteins or to the “protein package”, i.e. the other nutrients and substances tightly associated with protein, the metabolite markers of which also appear in the metabolic signature (6). However, recently, in a mediation study linking observance to healthy dietary patterns to prediabetes and type 2 diabetes, lower concentration of isoleucine has been identified among a relatively short list of potential mediators (7).

Although the exact mechanisms of altered BCAA concentrations and relationships to insulin resistance and T2D is yet to be determined, targeting BCAA metabolism as a therapeutic intervention in chronic diseases appears to be promising (8). Likewise, normalizing plasma glycine concentrations improves insulin sensitivity and thus, simple interventions such as dietary glycine supplementation may prove effective, although it is yet to be experimentally determined. Related to this is the fact that the simplest of amino acids from a structural point, glycine – a dispensable amino acid, has been shown to be a conditionally indispensable amino acid in infants in the past, and most recently in healthy pregnant women in later stages of pregnancy (9). Thus, it is likely that in disease there is a potential increase in the physiological requirement for glycine and needs to be quantitatively confirmed in future. Another so called ‘dispensable’ amino acid, arginine, is also intrinsically related to glycine through the enzyme L-arginine:glycine amidinotransferase (AGAT) to form guanidoacetic acid (GAA), which is the intermediary for the synthesis of creatine, a key energy metabolism regulator (10). AGAT is also involved in the formation of homoarginine (hArg) from arginine and lysine. Altered hArg plasma concentrations appear to be consistently associated with cardiovascular diseases, and with mortality or secondary events in cardiovascular diseases (11). However, it is unclear if supplementation with hArg is warranted unless a biological mechanism can be determined.

In patients with heart failure, dysregulation of the amino acid profile is common, with circulating concentrations of leucine, phenylalanine, tryptophan and methionine independently identified as risk factors (12). As yet, identifying diagnostic or risk modifier targets for amino acid concentrations/profile in heart failure is elusive. One major avenue of recent research discovery has been on microbial dysbiosis and the influence on production

of microbial gut amino acid derived metabolites, some of which are predictive of risk of cardiovascular events, such as Trimethylamine N-oxide (TMAO) and Indole-3 Propionate (IPA). TMAO is produced from L-carnitine, an amino acid derivative, and higher plasma concentrations are considered a risk factor for cardiovascular disease, while increased plasma IPA concentrations produced from tryptophan is considered as cardioprotective (13). Hydrogen sulfide (H₂S), a signaling molecule produced endogenously as well as from microbes in the large intestine plays a dual role – regulation of key body processes such as blood pressure, immunity etc., but in excess has been implicated in ulcerative colitis and colon cancer risk. Intakes of dietary protein enhances, while fiber intake reduces H₂S production (14). Whether a dietary intervention could regulate our gut microbial derived amino acid metabolites and generate a positive health outcome is yet unknown.

While the field of gut microbiome continues to generate new information, a few caveats need to be considered. An individual's gut microbiome is regulated by long term exposure to diet, environmental and pathogen exposure, diseases on the one hand, and short term impacts such as drugs including antibiotics on the other. Associations of microbiome with specific amino acid derived metabolites, in the absence of any known biological effect, does not provide causality and thus future studies need to focus on more in-depth analysis of cause and effect. Recently a deep metagenomic sequencing of microbiota combined with mass spectrometry-based metabolite profiling from a large human cohort with ages 50-64y showed that gut microbiota can explain up to 58% of the variance observed in plasma metabolites (15). Datasets such as these are valuable to continue to unravel the complex relationships between the microbiome and the host metabolism, understanding fully that at present we still cannot account for all the variability observed in human plasma amino acid concentrations. The hope is that more large-scale studies which make use of all 'omics' platforms with microbial deep metagenomic analysis and phenotyping individuals with a longitudinal follow up will be performed to help clarify associations identified thus far with altered plasma amino acids, and translate them to diagnostic and therapeutic modalities.

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