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EDITORIAL

Functional amino acids in nutrition and health

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Abstract The recent years have witnessed growing interest in biochemistry, physiology and nutrition of amino acids (AA) in growth, health and disease of humans and other animals. This results from the discoveries of AA in cell signaling involving protein kinases, G protein-coupled receptors, and gaseous molecules (i.e., NO, CO and H_2S). In addition, nutritional studies have shown that dietary supplementation with several AA (e.g., arginine, glutamine, glutamate, leucine, and proline) modulates gene expression, enhances growth of the small intestine and skeletal muscle, or reduces excessive body fat. These seminal findings led to the new concept of functional AA, which are defined as those AA that participate in and regulate key metabolic pathways to improve health, survival, growth, development, lactation, and reproduction of the organisms. Functional AA hold great promise in prevention and treatment of metabolic diseases (e.g., obesity, diabetes, and cardiovascular disorders), intrauterine growth restriction, infertility, intestinal and neurological dysfunction, and infectious disease (including viral infections).

Introduction

Amino acids (AA) are building blocks for tissue proteins and essential substrates for the synthesis of many low-molecular-weight substances (e.g., NO, polyamines, glutathione, creatine, carnitine, carnosine, thyroid hormones, serotonin, melanin, melatonin, and heme) with enormous physiological importance (Blachier et al. 2011; Kim et al. 2012; Kong et al. 2012; Wu 2009). Based on the growth or nitrogen balance of animals, AA have been traditionally classified as nutritionally "essential" or "nonessential" (see Wu 2009 for review). AA whose carbon skeletons are not synthesized de novo by animal cells must be provided in diets to sustain life and, therefore, are nutritionally essential (Table 1). Accordingly, cysteine and tyrosine, whose carbon skeletons are not synthesized de novo in animals, should be classified as nutritionally essential AA (Wu 2013). In contrast, AA that are synthesized de novo in animals have been previously thought to be dispensable in diets and, therefore, considered nutritionally "nonessential". However, nitrogen balance is not a sensitive indicator of optimal dietary AA requirements (Wu 2013). For example, adult men consuming an arginine-free diet can maintain a nitrogen balance for 9 days, but both the number and vitality of their sperm cells are decreased by 90 % (see Wu et al. 2009 for review). In addition, a lack of arginine from the maternal diet impairs embryonic/fetal survival and growth despite the absence of a negative nitrogen balance in the gestating swine (Wu et al. 2010). Indeed, there has been no compelling evidence for sufficient synthesis of nutritionally "nonessential" AA in humans and other animals (Li et al. 2009; Wu 2010).

Dietary requirements of AA depend on species, developmental stage, physiological status, the microbiota in the lumen of the small intestine, environmental factors, and pathological states (Dai et al. 2011, 2012a, b; Wu et al. 2013). Thus, some of the AA that are synthesized by animals have been classified as conditionally essential because rates of their utilization are greater than rates of their

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Table 1 Classification of AA in animal and human nutrition

Mammals[a]			Poultry			Fish		
EAA	NEAA	CEAA[b]	EAA	NEAA	CEAA[b]	EAA	NEAA	CEAA[b]
Arg[c]	Ala	Gln[c]	Arg[c]	Ala	Glnv	Arg[c]	Ala	Gln[c]
Cys[c]	Asn	Glu[c]	Cys[c]	Asn	Glu[c]	Cys[c]	Asn	Glu[c]
His	Asp[c]	Gly[c]	Gly[c]	Asp[c]	Tau[c]	His	Asp[c]	Gly[c]
Ile	Ser	Pro[c]	His	Ser		Ile	Ser	Tau[c]
Leu[c]		Tau[c]	Ile			Leu[c]		
Lys			Leu[c]			Lys		
Met[c]			Lys			Met[c]		
Phe			Met[c]			Phe		
Thr			Phe			Pro[c]		
Trp[c]			Pro[c]			Thr		
Tyr[c]			Thr			Trp[c]		
Val			Trp[c]			Tyr[c]		
			Tyr[c]			Val		
			Val					

Classification of AA as nutritionally '"essential" or "nonessential" or conditionally essential depends on species, age, physiological factors, environmental factors, and pathological states

CEAA conditionally essential AA, *EAA* nutritionally essential AA, *NEAA* nutritionally nonessential AA

[a] Preweaning ruminants have qualitatively similar requirements for dietary AA to those for nonruminants. In postweaning ruminants, the microbial source of protein and AA is inadequate for supporting their maximal growth or milk production when the animals are fed roughage diets

[b] For neonates (including human infants and piglets), adults under stress conditions (e.g., heat stress, burns, and infection), and breeding stocks (both males and females). Taurine (Tau) is a nutritionally essential AA for cats

[c] Functional AA

synthesis under certain conditions (e.g., early weaning, lactation, pregnancy, burns, injury, infection, heat stress, and cold stress) (Wu 2009). Examples include glutamine, arginine, proline, glycine and taurine for preterm human infants and weanling neonates (Table 1). Note that currently the major criterion for classification of conditionally essential AA is growth or N balance.

Some of the nutritionally "nonessential" AA (e.g., arginine, glutamine, glutamate, glycine, and proline for adults) play important roles in regulating gene expression (Kim et al. 2011a, b; Wu et al. 2011a, b) and micro-RNA levels (Liu et al. 2012), cell signaling (Bazer et al. 2012; Jewell et al. 2013), blood flow (Tan et al. 2012), nutrient transport and metabolism in animal cells (Suryawan et al. 2012; Wang et al. 2013), development of brown adipose tissue (Wu et al. 2012), intestinal microbial growth and metabolism (Dai et al. 2012a, b), anti-oxidative responses (Hou et al. 2012a, b), as well as innate and cell-mediated immune responses (Ren et al. 2011, 2013). Of particular interest, AA participate in and modulate cell signaling through: (1) several well-conserved protein kinases (including mammalian target of rapamycin, AMP-activated protein kinase, cGMP-dependent kinase, cAMP-dependent kinase, and mitogen-activated protein kinase), (2) G protein-coupled receptors, and (3) gaseous molecules, including NO, CO, and H_2S (Wu 2013). In addition, glutamate, glutamine, and aspartate [abundant AA in food proteins of plant and animal origin (Li et al. 2011a)] are major metabolic fuels for mammalian enterocytes (Burrin and Stoll 2009; Rezaei et al. 2013a, b). Emerging evidence shows a crucial role for glutamate in chemical sensing in the gastrointestinal tract (San Gabriel and Uneyama 2012) and possibly in other tissues (Gallinetti et al. 2013). Furthermore, these AA, along with glycine, tryptophan, tyrosine and D-amino acids (e.g., D-alanine, D-aspartate, and D-serine), regulate neurological development and function (Fernstrom 2012; Friedman and Levin 2012; Hou et al. 2012a, b; Wang et al. 2013). Moreover, leucine activates the mammalian target of rapamycin to stimulate protein synthesis and inhibit intracellular proteolysis (Dillon 2012; Li et al. 2011b), whereas methionine is the major donor of the methyl group to affect DNA and protein methylation in cells (Wang et al. 2012). Notably, nutritional studies have shown that dietary supplementation with several AA (e.g., arginine, glutamine, glutamate, leucine, and proline) modulates gene expression and enhances growth of the small intestine and skeletal muscle (Geng et al. 2011; Jobgen et al. 2009; Wang et al. 2008; Wu et al. 2011a, b;

Table 2 Roles of functional AA in nutrition and health

Building blocks for proteins, large peptides, and small peptides
Regulation of gene expression, as well as micro-RNA biogenesis and levels
Cell signaling via kinases (e.g., mammalian target of rapamycin, AMP-activated protein kinase, cGMP-dependent kinase, cAMP-dependent kinase, and mitogen-activated protein kinase), G protein-coupled receptors, and gaseous molecules (e.g., NO, CO and H_2S)
Nutrient transport and metabolism
Transport of water, amino acids, protein, glucose, fatty acids, vitamins, and minerals
Major energy substrates for the small intestine (glutamine, glutamate, and aspartate) and immunocytes (glutamine)
Substrates for, and activation of, protein synthesis
Inhibition of autophagy and intracellular protein degradation
Regulation of metabolism (activation of the oxidation of glucose and long-chain fatty acids to CO_2 and water; inhibition of glucose and fatty acid synthesis)
One-carbon unit metabolism and methylation of DNA and proteins
RNA and DNA synthesis, as well as amino acid, heme, and carnitine synthesis
Activation of lipolysis and reduction in white adipose tissue
Stimulation of brown adipose tissue development and thermogenesis
Appetite and body composition (e.g., skeletal muscle, fat, and bone masses)
Modulation of immune responses (T cell receptor, lymphocyte proliferation, the production of cytokines and antibodies, macrophage polarization to affect the population of M1 and M2 cells, killing of pathogens by NO, O_2^-, and H_2O_2) and prevention of infectious disease (including viral infections)
Lactation (synthesis of amino acids, proteins, lipids, and carbohydrates by mammary glands)
Reproduction (male and female fertility, fetal growth and development, and possibly fetal programming of postnatal metabolism and health)
Hormone secretion and endocrine status
Synthesis and secretion of hormones (e.g., thyroid hormones, insulin, glucagon, and glucocorticoids)
Mediation of hormone actions
Anti-oxidative defenses and removal of toxic substances
Synthesis of glutathione, carnosine, creatine, and taurine
Synthesis of antioxidative enzymes (e.g., glutathione peroxidase, superoxide dismutase and H_2O_2 peroxidase)
Removal of ammonia and xenobiotics
Anti-inflammation
Regulation of apoptosis and aging
Neurological function and behavior
Synthesis of neurotransmitters (e.g., serotonin, γ-aminobutyrate, dopamine, and acetylcholine)
Agonists and co-agonists of N-methyl-D-aspartic acid (e.g., glutamate, aspartate, glycine, D-aspartate, D-alanine, and D-serine)
Neuroprotective reactions
Digestive function
Chemical sensing via the G protein-coupled receptors in the gastrointestinal tract and possibly in other tissues
Gastrointestinal emptying and the motility of the small intestine
Conjugates with taurine and glycine to facilitate lipid digestion and absorption
Modulation of the growth, metabolism, and population of the microbiota in the lumen of the small intestine
Recovery from injury
Enhancement of wound healing after surgery or injury (e.g., polyamine and NO synthesis)
Synthesis of collagen and remodeling of extracellular matrix (e.g., glycine and proline)
Regulation of blood flow and cardiovascular function (e.g., NO synthesis)
Other physiological processes
Pigmentation (skin, hair, and eyes)
Regulation of acid–base balance (e.g., renal ammoniagenesis from glutamine)
Osmoregulation (e.g., taurine and glutamine in skeletal muscle, heart, and fetal fluids)
Metamorphosis of fish

Yao et al. 2008; Yin et al. 2010). The diverse and crucial roles of AA in metabolism, physiology, and immunity against infectious diseases (including viral infections) are truly remarkable (Table 2).

Based on the foregoing lines of compelling evidence from animal and human studies, Wu (2010) proposed the new concept of functional AA, which are defined as those AA that participate in and regulate key metabolic pathways to improve health, survival, growth, development, lactation, and reproduction of the organisms. Metabolic pathways include: (1) intracellular protein turnover (synthesis and degradation) and associated events (Bertrand et al. 2012; Kong et al. 2012; Wauson et al. 2013; Xi et al. 2011, 2012; Yao et al. 2012), (2) AA synthesis and catabolism (Brosnan and Brosnan 2012; Lei et al. 2012a, b), (3) generation of small peptides, nitrogenous metabolites, and sulfur-containing substances [e.g., H_2S (Mimoun et al. 2012)], (4) urea cycle and uric acid synthesis (Wu 2013), (5) lipid and glucose metabolism (Dai et al. 2013; Go et al. 2012; Satterfield et al. 2011, 2012), (6) one-carbon unit metabolism (Wang et al. 2012), and (7) cellular redox signaling (Hou et al. 2012a). Functional AA can be nutritionally "essential", "nonessential", or conditionally essential AA (Table 1). It is noteworthy that the concept of functional AA takes into consideration, the animal's metabolic needs for dietary AA beyond serving as the building blocks for proteins, large peptides, and small peptides. These new advances in AA nutrition are highlighted in the pages of this special issue of "Amino Acids" to further stimulate development of the field. Functional AA hold great promise in prevention and treatment of metabolic diseases (e.g., obesity, diabetes, and cardiovascular disorders), lactation failure, fetal and postnatal growth restriction, male and female infertility, organ (e.g., intestinal, neurological and renal) dysfunction, and infectious disease (including viral infections).

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Conflict of interest The author declares no conflict of interests.

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