

Amino acids: metabolism, functions, and nutrition

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Abstract Recent years have witnessed the discovery that amino acids (AA) are not only cell signaling molecules but are also regulators of gene expression and the protein phosphorylation cascade. Additionally, AA are key precursors for syntheses of hormones and low-molecular weight nitrogenous substances with each having enormous biological importance. Physiological concentrations of AA and their metabolites (e.g., nitric oxide, polyamines, glutathione, taurine, thyroid hormones, and serotonin) are required for the functions. However, elevated levels of AA and their products (e.g., ammonia, homocysteine, and asymmetric dimethylarginine) are pathogenic factors for neurological disorders, oxidative stress, and cardiovascular disease. Thus, an optimal balance among AA in the diet and circulation is crucial for whole body homeostasis. There is growing recognition that besides their role as building blocks of proteins and polypeptides, some AA regulate key metabolic pathways that are necessary for maintenance, growth, reproduction, and immunity. They are called functional AA, which include arginine, cysteine, glutamine, leucine, proline, and tryptophan. Dietary supplementation with one or a mixture of these AA may be beneficial for (1) ameliorating health problems at various stages of the life cycle (e.g., fetal growth restriction, neonatal morbidity and mortality, weaning-associated intestinal dysfunction and wasting syndrome, obesity, diabetes, cardiovascular disease, the metabolic syndrome, and infertility); (2) optimizing efficiency of metabolic transformations to enhance muscle growth, milk production, egg and meat quality and athletic performance, while preventing excess fat deposition and

reducing adiposity. Thus, AA have important functions in both nutrition and health.

Keywords Amino acids · Health · Metabolism · Nutrition

Abbreviations

AA	Amino acids
BCAA	Branched-chain amino acids
EAA	Nutritionally essential amino acids
eIF	Eukaryotic translation initiation factor
mTOR	Mammalian target of rapamycin
NEAA	Nutritionally non-essential amino acids
NO	Nitric oxide
PDV	Portal-drained viscera

Introduction

Amino acids (AA) are defined as organic substances containing both amino and acid groups. Except for glycine, all AA have an asymmetric carbon and exhibit optical activity. The absolute configuration of AA (L- or D-isomers) is defined with reference to glyceraldehydes. Except for proline, all protein AA have a primary amino group and a carboxyl group linked to the α -carbon atom (hence α -AA). In β -AA (e.g., taurine and β -alanine), an amino group links to the β -carbon atom. Post-translationally modified AA occur in some proteins (Galli 2007). Because of variations in their side chains, AA have remarkably different biochemical properties and functions (Brosnan 2001; Suenaga et al. 2008; Wu et al. 2007a). AA are generally stable in aqueous solution at physiological pH, except for (1) glutamine which is slowly

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cyclized to pyroglutamate (<1% per day at 1 mM at 25°C) and (2) cysteine which undergoes rapid oxidation to cystine.

Except for glycine, all AA can have L- and D-isomers. Most D-AA, except for D-arginine, D-cysteine, D-histidine, D-lysine, and D-threonine, can be converted into L-AA in animals via widespread D-AA oxidases and transaminases (Baker 2008; Fang et al. 2009). The efficiency of D-AA utilization, on a molar basis of the L-isomer, may be 20–100%, depending on substrates and species (Baker 2008).

Among more than 300 AA in nature, only 20 of them (α -AA) serve as building blocks of protein. However, non-protein α -AA (e.g., ornithine, citrulline, and homocysteine) and non- α AA (e.g., taurine and β -alanine) also play important roles in cell metabolism (Curis et al. 2007; Hu et al. 2008b; Manna et al. 2009; Perta-Kajan et al. 2007). Because of its large mass (representing 40–45% of body weight), skeletal muscle is the largest reservoir of both peptide-bound and free AA in the body (Davis and Fiorotto 2009). Over the past 20 years, much effort has been directed toward defining optimal requirements of AA by livestock species [including pigs (Wu et al. 2007a) and ruminants (Firkins et al. 2006)], birds (Baker 2008), fish (Li et al. 2008), and humans (Elango et al. 2009) under various nutritional, developmental, environmental, and pathological conditions. Additionally, results of recent studies indicate that the small intestine is

a major site for extensive catabolism of AA in humans and animals, therefore modulating the entry of dietary AA into the portal circulation and the pattern of AA in plasma (Riedijk et al. 2007; Stoll et al. 1998; Wu 1998). Further, there is growing interest in regulatory functions of L- and D-AA in nutrition and physiology (Kim and Wu 2008; Tujioka et al. 2007; Wang et al. 2008b), as well as the underlying cellular and molecular mechanisms (Grillo and Colombatto 2007; Jobgen et al. 2006; Katane et al. 2008; Scolari and Acosta 2007; Wang et al. 2008c).

Although each AA has its own unique catabolic pathway(s), the catabolism of many AA exhibit a number of common characteristics in organisms (Table 1). Important metabolites of AA include ammonia, CO₂, long-chain and short-chain fatty acids, glucose, H₂S, ketone bodies, nitric oxide (NO), urea, uric acid, polyamines, and other nitrogenous substances with enormous biological importance (Blachier et al. 2007; Montanez et al. 2008; Morris 2007; Rider et al. 2007; Sugita et al. 2007) (Table 2). Complete oxidation of AA carbons occurs only if their carbons are ultimately converted to acetyl-CoA, which is oxidized to CO₂ and H₂O via the Krebs cycle and mitochondrial electron transport system. On a molar basis, oxidation of AA is less efficient for ATP production, compared with fat and glucose (Table 3). Thus, the efficiency of energy transfer from L-AA to ATP ranges from 29% for methionine to 59%

Table 1 Reactions initiating AA catabolism in animals

Reactions	Examples	
Transamination	Leucine + α ketoglutarate \leftrightarrow α ketoisocaproate + glutamate	(1)
Deamidation	Glutamine + H ₂ O \rightarrow glutamate + NH ₄ ⁺	(2)
Oxidative deamination	Glutamate + NAD ⁺ \leftrightarrow α ketoglutarate + NH ₃ + NADH + H ⁺	(3)
Decarboxylation	Ornithine \rightarrow putrescine + CO ₂	(4)
Hydroxylation	Arginine + O ₂ + BH ₄ + NADPH + H ⁺ \rightarrow NO + BH ₄ + citrulline + NADP ⁺	(5)
Reduction	Lysine + α ketoglutarate + NADPH + H ⁺ \rightarrow saccharopine + NADP ⁺	(6)
Dehydrogenation	Threonine + NAD ⁺ \rightarrow 2 amino 3 ketobutyrate + NADH + H ⁺	(7)
Hydrolysis	Arginine + H ₂ O \rightarrow ornithine + urea	(8)
Dioxygenation	Cysteine + O ₂ \rightarrow cysteinesulfinate	(9)
One carbon unit transfer	Glycine + MTHF \leftrightarrow serine + THF	(10)
Condensation	Methionine + Mg ATP \rightarrow S adenosylmethionine + Mg PPi + Pi	(11)
Oxidation	Proline + 1/2 O ₂ \rightarrow pyrroline 5 carboxylate + H ₂ O	(12)
Amidotransferation	Glutamine + F6P \leftrightarrow glucosamine 6 phosphate + glutamate	(13)
Deaminated oxidation	D Amino acid + O ₂ + H ₂ O \leftrightarrow α ketoacid + H ₂ O ₂ + NH ₃	(14)
Dehydration	Serine \rightarrow aminoacrylate + H ₂ O	(15)
Cleavage	Glycine + NAD ⁺ + THF \leftrightarrow MTHF + CO ₂ + NH ₃ + NADH + H ⁺	(16)

Enzymes that catalyze the indicated reactions are: (1) BCAA transaminase; (2) phosphate activated glutaminase; (3) glutamate dehydrogenase; (4) ornithine decarboxylase; (5) NO synthase; (6) lysine: α ketoglutarate reductase; (7) threonine dehydrogenase; (8) arginase; (9) cysteine dioxygenase; (10) hydroxymethyltransferase; (11) S adenosylmethionine synthase; (12) proline oxidase; (13) glutamine:fructose 6 phosphate transaminase; (14) D amino acid oxidase; (15) serine dehydratase; (16) glycine synthase (glycine cleavage system). F6P fructose 6 phosphate, MTHF N⁵ N¹⁰ methylene THF, THF tetrahydrofolate. BH₄, tetrahydrobiopterin (required for hydroxylation of arginine, phenylalanine, tyrosine, and tryptophan)

Table 2 Major metabolites and functions of AA in nutrition and metabolism

AA	Products	Major functions
AA	Directly	Protein synthesis; osmolytes; regulation of hormone secretion, gene expression and cell signaling
Alanine	Directly	Inhibition of pyruvate kinase and hepatic autophagy; gluconeogenesis; transamination; glucose alanine cycle
β Alanine	Directly	A component of coenzyme A and pantothenic acid
	Dipeptides	Carnosine (β alanyl L histidine), carcaine (β alanyl histamine), anserine (β alanyl 1 methyl L histidine), and balenine (β alanyl 3 methyl histidine) with antioxidative function
Arginine	Directly	Activation of mTOR signaling; antioxidant; regulation of hormone secretion; allosteric activation of NAG synthase; ammonia detoxification; regulation of gene expression; immune function; activation of BH ₄ synthesis; N reservoir; methylation of proteins; deimination (formation of citrulline) of proteins ^a
	NO	Signaling molecule; regulator of nutrient metabolism, vascular tone, hemodynamics, angiogenesis, spermatogenesis, embryogenesis, fertility, immune function, hormone secretion, wound healing, neurotransmission, tumor growth, mitochondrial biogenesis, and function
	Agmatine	Inhibition of NOS, ODC, and monoamine oxidase; ligand for α_2 adrenergic and imidazoline receptors
	Ornithine	Ammonia detoxification; syntheses of proline, glutamate, and polyamines; mitochondrial integrity; wound healing
	Methylarginines	Competitive inhibition of NOS
Asparagine	Directly	Cell metabolism and physiology; regulation of gene expression and immune function; ammonia detoxification; function of the nervous system
	Acrylamide ^b	Oxidant; cytotoxicity; gene mutation; food quality
Aspartate	Directly	Purine, pyrimidine, asparagine, and arginine synthesis; transamination; urea cycle; activation of NMDA receptors; synthesis of inositol and β alanine
Citrulline	Directly	Antioxidant; arginine synthesis; osmoregulation; ammonia detoxification; N reservoir
Cysteine	Directly	Disulfide linkage in protein; transport of sulfur
	Taurine	Antioxidant; regulation of cellular redox state; osmolyte
	H ₂ S	A signaling molecule
Glutamate	Directly	Glutamine, citrulline, and arginine synthesis; bridging the urea cycle with the Krebs cycle; transamination; ammonia assimilation; flavor enhancer; activation of NMDA receptors; NAG synthesis
	GABA	Excitatory neurotransmitter; inhibition of T cell response and inflammation
Glutamine	Directly	Regulation of protein turnover through cellular mTOR signaling, gene expression, and immune function; a major fuel for rapidly proliferating cells; inhibition of apoptosis; syntheses of purine, pyrimidine, ornithine, citrulline, arginine, proline, and asparagines; N reservoir; synthesis of NAD(P)
	Glu and Asp	Excitatory neurotransmitters; components of the malate shuttle; cell Metabolism; ammonia detoxification; major fuels for enterocytes
	Glucosamine 6 P	Synthesis of aminosugars and glycoproteins; inhibition of NO synthesis
	Ammonia	Renal regulation of acid base balance; synthesis of glutamate and CP
Glycine	Directly	Calcium influx through a glycine gated channel in the cell membrane; purine and serine synthesis; synthesis of porphyrins; inhibitory neurotransmitter in CNS; co agonist with glutamate for NMDA receptors
	Heme	Hemoproteins (e.g., hemoglobin, myoglobin, catalase, and cytochrome c); production of CO (a signaling molecule)
Histidine	Directly	Protein methylation; hemoglobin structure and function; antioxidative dipeptides; one carbon unit metabolism
	Histamine	Allergic reaction; vasodilator; central acetylcholine secretion; regulation of gut function
	Urocanic acid	Modulation of the immune response in skin
Isoleucine	Directly	Synthesis of glutamine and alanine; balance among BCAA
Leucine	Directly	Regulation of protein turnover through cellular mTOR signaling and gene expression; activator of glutamate dehydrogenase; BCAA balance; flavor enhancer
	Gln and Ala	Interorgan metabolism of nitrogen and carbon
	HMB	Regulation of immune responses
Lysine	Directly	Regulation of NO synthesis; antiviral activity (treatment of Herpes simplex); Protein methylation (e.g., trimethyllysine in calmodulin), acetylation, ubiquitination, and O linked glycosylation
	OH lysine	Structure and function of collagen
Methionine	Homocysteine	Oxidant; independent risk factor for CVD; inhibition of NO synthesis
	Betaine	Methylation of homocysteine to methionine; one carbon unit metabolism
	Choline	Synthesis of betaine, acetylcholine, phosphatidylcholine, and sarcosine
	Cysteine	Cellular metabolism and nutrition
	DCSAM	Methylation of proteins and DNA; polyamine synthesis; gene expression
	Taurine	Antioxidant; osmoregulation; organ development; vascular, muscular, cardiac, and retinal functions; anti inflammation
	Phospholipids	Synthesis of lecithin and phosphatidylcholine cell signaling
Phenylalanine	Directly	Activation of BH ₄ (a cofactor for NOS) synthesis; synthesis of tyrosine; neurological development and function

Table 2 continued

AA	Products	Major functions
Proline	Directly	Collagen structure and function; neurological function; osmoprotectant
	H ₂ O ₂	Killing pathogens; intestinal integrity; a signaling molecule; immunity
	P5C	Cellular redox state; DNA synthesis; lymphocyte proliferation; ornithine, citrulline, arginine and polyamine synthesis; gene expression; stress response
	OH proline	Structure and function of collagen
Sarcosine	Directly	An intermediate in the synthesis of glycine from choline; possible treatment of certain mental disorders; a source of formaldehyde and H ₂ O ₂ ; inhibition of glycine transport
Serine	Directly	One carbon unit metabolism; syntheses of cysteine, purine, pyrimidine, ceramide and phosphatidylserine; synthesis of tryptophan in bacteria; gluconeogenesis (particularly in ruminants); protein phosphorylation
	Glycine D Serine ^c	Antioxidant; one carbon unit metabolism; neurotransmitter Activation of NMDA receptors in brain
Theanine	Directly	An amino acid (glutamine analog) in tea leaves; antioxidant; increasing levels of GABA, dopamine, and serotonin in brain; neuroprotective effect
Threonine	Directly	Synthesis of the mucin protein that is required for maintaining intestinal integrity and function; immune function; protein phosphorylation and O linked glycosylation; glycine synthesis
Tryptophan	Serotonin	Neurotransmitter; inhibiting production of inflammatory cytokines and superoxide
	NAS	Inhibitor of BH ₄ synthesis; antioxidant; inhibition of the production of inflammatory cytokines and superoxide
	Melatonin	Antioxidant; inhibition of the production of inflammatory cytokines and superoxide
	ANS	Inhibiting production of proinflammatory T helper 1 cytokines; preventing autoimmune neuroinflammation; enhancing immune function
	Niacin	A component of NAD and NADP, coenzymes for many oxidoreductases
Tyrosine	Directly	Protein phosphorylation, nitrosation, and sulfation
	Dopamine	Neurotransmitter; regulation of immune response
	EPN and NEPN	Neurotransmitters; cell metabolism
	Melanin	Antioxidant; inhibition of the production of inflammatory cytokines and superoxide
Valine	Directly	Synthesis of glutamine and alanine; balance among BCAA
Arg and Met	Polyamines	Gene expression; DNA and protein synthesis; ion channel function; apoptosis; signal transduction; antioxidants; cell function; cell proliferation and differentiation
Arg, Met, and Gly	Creatine	Antioxidant; antiviral; antitumor; energy metabolism in muscle and brain; neurological and muscular development and function
Cys, Glu, and Gly	Glutathione	Free radical scavenger; antioxidant; cell metabolism (e.g., formation of leukotrienes, mercapturate, glutathionylspermidine, glutathione NO adduct and glutathionylproteins); signal transduction; gene expression; apoptosis; cellular redox; immune response
Gln, Asp, Gly, and Ser	Nucleic acids	Coding for genetic information; gene expression; cell cycle and function; protein and uric acid synthesis; lymphocyte proliferation
	Uric acid	Antioxidant; the major end product of amino acid oxidation in avian species
Lys, Met, and Ser	Carnitine	Transport of long chain fatty acids into mitochondria for oxidation; storage of energy as acetylcarnitine; antioxidant

ANS anthranilic acid, BCAA branched chain AA, BH₄ tetrahydrobiopterin, CNS central nervous system, CP carbamoylphosphate, CVD cardiovascular disease, DCSAM decarboxylated S adenosylmethionine, EPN epinephrine, GABA γ aminobutyrate, HMB β hydroxy β methylbutyrate, NAG N acetylglutamate, NAS N acetylserotonin, NEPN norepinephrine, NOS NO synthase, ODC ornithine decarboxylase, P5C pyrroline 5 carboxylate, Tau-Cl taurine chloramine

^a Including myelin basic protein, filaggrin, and histone proteins

^b Formed when asparagine reacts with reducing sugars or reactive carbonyls at high temperature

^c Synthesized from L serine by serine racemase

for isoleucine. However, glutamine is a preferred major fuel for rapidly dividing cells, including enterocytes, lymphocytes, macrophages, and tumors (Curthoys and Watford 1995; Rhoads et al. 1997). The major objective of this article is to provide insights into new developments in AA nutrition research, as well as their implications for both nutrition and health.

Definitions of essential, non-essential, and functional AA

On the basis of needs from the diet for nitrogen balance or growth, AA were traditionally classified as nutritionally essential (indispensable) or non-essential (dispensable) for humans and animals (Table 4). Essential AA (EAA) are

Table 3 Energetic efficiency of oxidation of amino acids, protein, and other substrates in animals

Nutrients	Combustion energy ^a		Net atp production		Efficiency of energy transfer to ATP ^b (%)
	kJ per		mol per		
	mol AA	g AA	mol AA	g AA	
Alanine	1,577	17.7	16	0.180	52.4
Arginine	3,739	21.5	29	0.167	40.0
Asparagine	1,928	14.6	14	0.106	37.5
Aspartate	1,601	12.0	16	0.120	51.6
Cysteine	2,249	18.6	13	0.107	29.8
Glutamate	2,244	15.3	25	0.170	57.5
Glutamine	2,570	17.6	23	0.157	46.2
Glycine ^c	973	13.0	13	0.173	68.9
Histidine	3,213	20.7	21	0.135	33.7
Isoleucine	3,581	27.3	41	0.313	59.1
Leucine	3,582	27.3	40	0.305	57.6
Lysine	3,683	25.2	35	0.239	49.0
Methionine	3,245	23.0	18	0.121	28.6
Ornithine	3,030	22.9	29	0.219	49.4
Phenylalanine	4,647	28.1	39	0.236	43.3
Proline	2,730	23.7	30	0.261	56.7
Serine	1,444	13.7	13	0.124	46.5
Threonine	2,053	17.2	21	0.176	52.8
Tryptophan	5,628	27.6	38	0.186	34.8
Tyrosine	4,429	24.4	42	0.232	48.9
Valine	2,922	25.0	30	0.256	53.0
Protein ^d	2,486	22.6	24	0.218	49.8
Glucose	2,803	15.6	38	0.211	70.0
Starch ^e	2,779	17.2	38	0.235	70.6
Palmitate	9,791	38.2	129	0.504	68.0
Fat ^f	31,676	39.3	409	0.507	66.6

^a Adapted from Cox (1970)

^b Calculated on the basis of 51.6 kJ/mol for one high energy bond in ATP (moles of net ATP production/mol substrate × 51.6 kJ/mol ÷ combustion energy of kJ/mol substrate × 100)

^c When 1 mol glycine is catabolized by the glycine cleavage system, 1 mol ATP is produced. When 1 mol glycine is converted to serine and then oxidized, 13 mol ATP are produced

^d Assuming that the average molecular weight of an AA residue in protein is 110

^e The average molecular weight of glucose residue in starch is 162

^f Tripalmitoylglycerol is used as an example

defined as either those AA whose carbon skeletons cannot be synthesized or those that are inadequately synthesized de novo by the body relative to needs and which must be provided from the diet to meet optimal requirements. Conditionally essential AA are those that normally can be synthesized in adequate amounts by the organism, but which must be provided from the diet to meet optimal needs under conditions where rates of utilization are greater than rates of synthesis. However, functional needs (e.g., reproduction and disease prevention) should also be a

criterion for classification of essential or conditionally essential AA. Non-essential AA (NEAA) are those AA which can be synthesized de novo in adequate amounts by the body to meet optimal requirements. It should be recognized that all of the 20 protein AA and their metabolites are required for normal cell physiology and function (El Idrissi 2008; Lupi et al. 2008; Novelli and Tasker 2008; Phang et al. 2008). Abnormal metabolism of an AA disturbs whole body homeostasis, impairs growth and development, and may even cause death (Orlando et al.

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