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INVITED REVIEW

Dietary requirements of "nutritionally non-essential amino acids" by animals and humans

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Abstract Amino acids are necessary for the survival, growth, development, reproduction and health of all organisms. They were traditionally classified as nutritionally essential or non-essential for mammals, birds and fish based on nitrogen balance or growth. It was assumed that all "non-essential amino acids (NEAA)" were synthesized sufficiently in the body to meet the needs for maximal growth and health. However, there has been no compelling experimental evidence to support this assumption over the past century. NEAA (e.g., glutamine, glutamate, proline, glycine and arginine) play important roles in regulating gene expression, cell signaling, antioxidative responses, neurotransmission, and immunity. Additionally, glutamate, glutamine and aspartate are major metabolic fuels for the small intestine to maintain its digestive function and protect its mucosal integrity. Therefore, based on new research findings, NEAA should be taken into consideration in revising the classical "ideal protein" concept and formulating balanced diets to improve protein accretion, food efficiency, and health in animals and humans.

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Abbreviations

AA	Amino acids
AMPK	AMP-activated protein kinase
EAA	Nutritionally essential amino acids
4EBP1	Eukaryotic translation initiation factor 4E-binding protein-1
MTOR	Mechanistic target of rapamycin
NEAA	Nutritionally non-essential amino acids
NO	Nitric oxide
NRC	National Research Council

Introduction

Adequate provision of dietary amino acids (AA) is essential for the health, growth, development and survival of animals and humans (Ren et al. 2012; Wu 2009). Based on growth or nitrogen balance, AA have traditionally been classified as nutritionally essential (indispensable) or non-essential (dispensable) for mammals, birds and fish (Le Ple'nier et al. 2012); Liu et al. 2012; Obayashi et al. 2012). Nutritionally essential AA (EAA) are defined as either those AA whose carbon skeletons cannot be synthesized de novo *in animal cells* or those that *normally* are insufficiently synthesized de novo by the animal organism relative to its needs for maintenance, growth, development, and health and which must be provided in the diet to meet the requirements (Wu 2010). In contrast, nutritionally non-essential AA (NEAA) are those AA which can be synthesized de novo in adequate amounts by the animal organism

to meet the requirements for maintenance, growth, development and health and, therefore, need not be provided in the diet. To date, there is no compelling evidence for sufficient synthesis of all AA that are currently not classified as EAA in animal nutrition. Clearly, the terms EAA and NEAA are only the matters of definitions. However, guided by the concept of "nutritional non-essentiality", nutritionists have long ignored NEAA in dietary formulation. The major objective of this article is to bring, into readers'attention, the conceptual and practical limitations of the NEAA definition and to propose the needs for dietary NEAA by animals and humans.

Physiological roles of NEAA in nutrition

Amino acids have multiple roles in animal physiology (Fig. 1). First, AA regulates gene expression, which is defined as the translation of information encoded in a gene into ribonucleic acid (RNA: including messenger, transfer, and ribosomal RNA) and protein (Wang et al. 2012). This is a highly specific process in which a gene can be switched on or off in response to the regulatory factors. Besides serving as substrates for protein synthesis, AA affect one or more of the following steps: modification of chromatin (the complex of DNA and covering proteins, such as histones), transcription (synthesis of mRNA from DNA), post-transcriptional modification, RNA transport, mRNA degradation, translation (synthesis of protein/polypeptides from mRNA), and post-translational modifications (Brasse-Lagnel et al. 2009; Bruhat et al. 2009). Five of the most studied NEAA are arginine, glutamine, glutamate, glycine, and proline (Boutry et al. 2012; Lei et al. 2012; Mateo et al. 2007; Shi et al. 2012; Wu et al. 2011a; Yao et al. 2012). For example, arginine activates the mechanistic target of rapamycin (MTOR) signaling pathway to stimulate muscle protein synthesis in young pigs (Yao et al. 2008), an animal model widely used to study the human nutrition and metabolism (Hou et al. 2012; Tan et al. 2012; Wilson et al. 2011). Also, results of our microarray studies involving early-weaned pigs supplemented with or without glutamine indicated that early weaning resulted in increased (52–346 %) expression of genes related to oxidative stress and immune activation, but decreased (35–77 %) expression of genes related to macronutrient metabolism and proliferation of cells in the gut (Wang et al. 2008). Dietary glutamine supplementation increased intestinal expression (120–124 %) of genes that are necessary for cell growth and removal of oxidants, while reducing (34–75 %) expression of genes that promote oxidative stress and immune activation (Wang et al. 2008). In addition, glutamine enhances the MTOR signaling and protein synthesis in both skeletal muscle (Xi et al. 2011) and small intestine (Xi et al. 2012). These findings reveal coordinate alterations of gene expression in response to weaning and aid in providing molecular mechanisms for the beneficial effects of dietary glutamine supplementation to improve the nutritional status in young mammals (Fig. 2).

Second, NEAA regulate the synthesis of nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S), which participate in gaseous signaling in cells through cGMP and cAMP production to enhance blood flow, nutrient transport, protein deposition, and immunity (Li et al. 2009). In particular, glycine is the precursor of heme, oxidation of which yields CO, whereas cysteine is the substrate for H_2S generation. NO is synthesized from arginine by one of the three isoforms of NO synthase (NOS): neuronal NOS (nNOS also known as NOS1), inducible NOS (iNOS also known as NOS2), and endothelial NOS (eNOS also known as NOS3) (Oess et al. 2006). Many NEAA have been reported to regulate the production of NO, CO, and H_2S in a cell-dependent manner (Li et al. 2009; Wu and Meininger 2002). For example, arginine, citrulline, glutamate, glycine, taurine and γ-aminobutyrate increase NO synthesis by constitutive NOS in endothelial cells or brain, whereas glutamine inhibits NO generation by both constitutive and inducible NOSs (Flynn et al. 2005). Furthermore, arginine, glutamine, glutamate, alanine, taurine, and glycine promotes CO synthesis by heme oxygenase in endothelial cells and non-vascular tissues, but *N*-acetyl-cysteine attenuates CO formation in injured brain and vascular smooth muscle cells (Li et al. 2009). Thus, inadequate production of NO, CO and H_2S will impair whole-body insulin sensitivity and the efficiency of nutrient utilization for protein accretion.

Third, NEAA (e.g., arginine, glutamate, glutamine, and proline) participate in cell signaling pathways involving MTOR, cAMP-dependent kinases, cGMP-dependent kinases, G-protein coupled receptors, AMPK, mitogen-activated protein kinases (MAPK) (Chiu et al. 2012; Ray et al. 2012; Rhoads et al. 2000, 2008; Wu et al. 2011a). These are complex networks of metabolic regulation, but they are all regulated by protein phosphorylation and protein

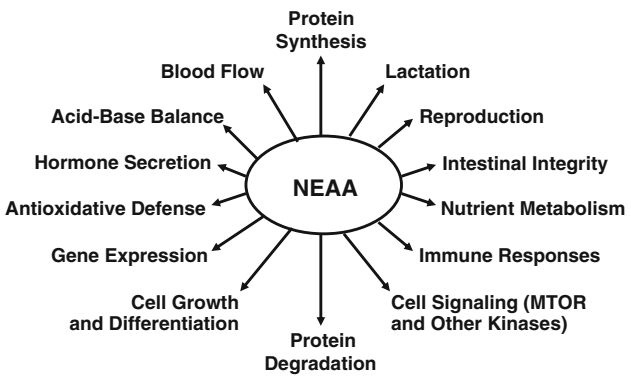

Fig. 1 Physiological functions of NEAA in animals

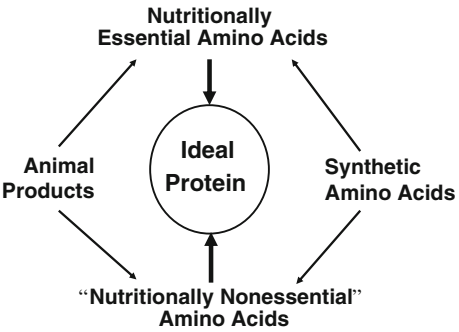

Fig. 2 Modification of the "ideal protein" concept by including dietary NEAA requirements for animals. Like EAA, supplemental NEAA can be provided either as synthetic AA or from animal protein ingredients

dephosphorylation mechanisms (Wu 2010). These pathways also involve activation of various proteins in the cytoplasm and the nucleus to regulate cellular processes, including (1) gene expression; (2) nutrient metabolism; (3) cell proliferation, differentiation, and migration; (4) mitosis and cell survival; (5) cell cycle progression; (6) cell survival and apoptosis; and (7) inflammatory responses (Clemmensen et al. 2012; Go et al. 2012; Zhou et al. 2012).

Fourth, NEAA are substrates for the synthesis of many nitrogenous substances with important functions (Wu 2009). Some of these bioactive molecules include carnosine, creatine, glutathione, neurotransmitters, polyamines, taurine, and low-molecular-weight hormones (del Favero et al. 2012; Ito et al. 2012; Jung et al. 2012; Peters et al. 2012). They are all essential for the growth, lactation, reproduction, health, and survival of animals, including humans. Examples include: (1) nutrient absorption and metabolism (e.g., nutrient transport, protein turnover, fat synthesis and oxidation, glucose synthesis and oxidation, AA synthesis and oxidation, urea and uric synthesis for ammonia detoxification, and efficiency of food utilization); (2) regulation of endothelial cell function, blood flow, lymph circulation, as well as immune function and health (e.g., T cell proliferation and B cell maturation, antibody production by B-cells, killing of pathogens, obesity, diabetes, and metabolic syndrome); (3) spermatogenesis, male fertility, ovulation, ovarian steroidogenesis, embryonic implantation and survival, placental angiogenesis and growth, fetal growth and development, and lactogenesis); (4) acid–base balance, neurotransmission, extracellular and intracellular osmolarity, antioxidative defense, and whole-body homeostasis; (5) post-natal survival, growth and development, and (6) the development, regeneration and remodeling of tissues, including brown adipose tissue and the vasculature (Brosnan and Brosnan 2010; Kimura 2010; Satterfield et al. 2011, 2012; Wu et al. 2012).

Fifth, NEAA can regulate the utilization of dietary protein by bacteria in the lumen of small intestine, thereby affecting its nutritive value in animals (Dai et al. 2011). Analysis of AA composition and the incorporation of AA into polypeptides has shown that protein synthesis is a major pathway for AA metabolism in all the porcine intestinal lumen bacteria studied (Dai et al. 2010). Of particular interest, arginine and glutamine play roles in modulating AA metabolism by intestinal microbes. For example, arginine increases the net utilization of threonine, glycine, phenylalanine, and branched-chain AA by *Streptococcus* sp. and *Klebsiella* sp., while decreasing the net utilization of lysine, threonine, isoleucine, leucine, glycine and alanine by jejunal or ileal mixed bacteria (Dai et al. 2012a). Furthermore, glutamine reduces net utilization of asparagine, lysine, leucine, valine, ornithine and serine by jejunal or ileal mixed bacteria (Dai et al. 2012b, c). These results have important implications for developing new means to formulate diets for animals.

Dietary requirements of NEAA

Dietary requirements of NEAA should be based on the metabolic needs of *all* AA for the maintenance, tissue protein synthesis, generation of physiologically important non-protein metabolites, and their regulatory functions (Fig. 2). Thus, dietary NEAA requirements likely vary with nutritional, physiological, pathological, and environmental factors (Wu 2010). Deng et al. (2009) have reported that, in young pigs fed diets containing the same amount of EAA, reduced dietary content of NEAA limits tissue protein synthesis and growth performance (Table 1). Despite the recognition that NEAA play essential roles in growth, lactation, reproduction, and health (Wu 2010), the recent edition of the National Research Council (NRC 2012)'s nutrient requirements of swine did not recommend dietary requirements of any NEAA for pigs at any developmental stage. NRC (2012) indicated that typically, swine have sufficient capacity for the synthesis of all NEAA and do not require these AA from diets. However, ample evidence from recent studies is inconsistent with this notion (Wu 2009, 2010). Furthermore, synthesis of NEAA in the animal organism critically depends on the availability of EAA that are usually provided from protein in expensive ingredients, and *sufficient capacity* does not necessarily translate into *sufficient synthesis* of NEAA in pigs fed with an ordinary diet to minimize production costs. Likewise, the Institute of Medicine (2005) stated that dietary arginine was not required by the healthy adults because arginine is synthesized via the hepatic urea cycle. However, there is no *net* synthesis of arginine in the mammalian liver via the hepatic urea cycle (Wu and Morris 1998). This demonstrates the importance of ensuring that recommendations for dietary NEAA requirements be based on up-to-date

Table 1 Deficiency of NEAA limits tissue protein synthesis and growth of piglets (25–39 days) fed a low-protein diet

	Dietary protein content		
	20.7 %	12.7 % + EAA[a]	Pooled SEM
Protein synthesis (%/day)			
Longissimus muscle	11.8	7.1*	0.8
Liver	83.5	63.0*	4.2
Kidney	36.1	24.1*	1.6
Pancreas	76.4	62.7*	2.3
Feed intake (FI; g/day)	432	455	50
Body-weight gain (g/day)	299	264*	10
Feed:Gain ratio (g/g)	1.44	1.72*	0.02

Adapted from Deng et al. (2009). Beginning at 25 days of age, post-weaning pigs were fed a corn- and soybean meal-based diet for 14 days. Data are mean ± SEM, $n = 6$. * $P < 0.05$ vs the control (20.7 % protein) group

[a] EAA (Lys, Met, Thr, Trp, Leu, Ile, and Val) were added to the low-protein diet, so that both diets had the same amounts of all EAA. However, the low-protein diet provided less amounts of NEAA than the 20.7 % crude-protein diet

knowledge of new developments in the field of AA metabolism.

The fact that some AA can be synthesized in the body at the expense of considerable amounts of energy speaks highly for their physiological importance (Reeds 2000). Therefore, pathways for their de novo syntheses have evolved or have been highly conserved in the body. Likewise, all NEAA undergo metabolic transformations and have crucial physiological functions. For example, the unusually high concentration (~1 mM) of glycine in the plasma of post-natal pigs has an important role in stimulating rapid growth (Flynn et al. 2000), and the abundance of arginine (up to 6 mM) in porcine allantoic fluid during early gestation promotes placental growth (including placental angiogenesis) and fetal development (Wu et al. 2006). Thus, there is compelling evidence that an inadequate supply of NEAA in the diet impairs growth and production performance of swine (Wu et al. 2010, 2011b). For example, results of recent studies indicate that (1) diets must contain sufficient amounts of arginine and glutamine to support optimal fetal, neonatal and post-weaning growth in pigs (Kim and Wu 2004, 2009; Wu et al. 2004, 2010, 2011b); and (2) dietary supplementation with proline (Kirchgessner et al. 1995; Wu et al. 2011a) or glutamate (Rezaei et al. 2012) enhances growth performance and feed efficiency of early-weaned pigs. Based on the whole-body oxidation of phenylalanine fed a milk protein-based diet, Ball et al. (1986) have suggested that proline is an EAA for young pigs.

Recommendations of dietary NEAA requirements for animals depend on the expected levels of their growth, reproduction, and in the case of livestock and poultry, also production performance. Based on published studies, Table 2 lists our recommended total levels of arginine, glutamine, glutamate, and proline in typical corn- and soybean meal-based diets for gestating and lactating sows, as well as post-weaning and growing-finishing swine. This can provide an example for estimating dietary NEAA requirements by other species including humans. Supplemental NEAA needed to meet the dietary requirements can be supplied either as synthetic AA (Davis and Fiorotto 2009; Go et al. 2012; Wu et al. 1996) or from animal products that are excellent sources of both EAA and NEAA (Li et al. 2011). The composition of AA in common ingredients for animal diets (Li et al. 2011) differs substantially from that in animal body proteins (Table 3). This knowledge can greatly facilitate the dietary formulations to meet requirements for all AA, including EAA and NEAA (Wu 2010).

Based on the composition of EAA in animals (primarily the carcass), the "ideal protein" concept (optimal proportions

Table 2 Recommendations of dietary NEAA requirements for swine

NEAA and criteria	Gestating sows (Mateo et al. 2007; Wu et al. 2010)	Lactating sows (Mateo et al. 2008; Wu et al. 2011a)	Post-weaning piglets (Tan et al. 2009a; Wang et al. 2008)	Growing-finishing pigs (Tan et al. 2009b; Tan et al. 2011)
% of diet (as-fed basis; typical corn- and soybean meal-based diet)				
Arginine	1.13[a], 1.53[b]	1.90	2.04	2.25
Glutamine	1.22[a], 2.22[b]	2.72	2.71	1.65
Glutamate	1.07[a], 1.57[b]	2.51	2.62	1.40
Proline	1.03[a], 1.53[b]	2.37	2.58	1.38
Criteria	Litter size	Milk production	Digestion	Muscle growth
	Fetal growth	Piglet growth	Piglet growth	Meat quality
	Feed efficiency	Feed efficiency	Feed efficiency	Feed efficiency
	Immunity	Immunity	Growth	Immunity

[a] Before day 90 of gestation; feed intake = 2 kg/sow/day

[b] After day 90 of gestation; feed intake = 2 kg/sow/day

Table 3 Composition of AA in the bodies of animals

Amino acid	Rat[a]	Human[b]	Cattle[b]	Sheep[c]	Chick[d]	Pig	
mg AA/G protein						Intact[e] AA	AA[f] residue
Alanine	66.0	72	76	66.5	66.3	65.7	61.6
Arginine	68.2	77	75	68.0	68.5	67.7	71.4
Asparagine	36.5	–	–	35.8	36.5	36.0	36.5
Aspartate	43.4	–	–	43.7	43.1	42.8	43.6
Asp + Asn	79.9	90	87	79.5	79.6	78.8	80.1
Cysteine	14.5	–	–	14.6	15.0	13.2	13.2
Glutamine	51.0	–	–	50.9	50.5	51.2	52.8
Glutamate	83.8	–	–	83.2	82.9	84.6	87.0
Glu + Gln	135	130	138	134	133	136	140
Glycine	114	118	121	113	115	117	105
Histidine	21.0	26	27	21.2	21.1	20.8	21.6
Isoleucine	35.7	35	30	36.0	35.9	35.3	35.9
Leucine	69.0	75	74	69.4	69.2	68.3	69.3
Lysine	61.8	72	69	61.0	61.5	60.3	62.2
Methionine	19.2	20	18	19.0	18.9	18.7	19.3
Phenylalanine	34.1	41	39	34.6	34.8	34.3	35.9
Proline	85.7	84	87	85.5	85.3	86.1	85.3
OH-Pro	34.6	–	–	34.8	34.8	37.9	38.5
Pro + OH-Pro	120	–	–	120	120	124	124
Serine	44.8	44	47	45.2	45.0	44.3	43.1
Threonine	36.0	41	43	36.8	36.3	35.1	35.0
Tryptophan	12.0	–	–	11.4	11.6	11.1	11.9
Tyrosine	26.8	29	27	27.0	26.6	27.2	28.6
Valine	42.0	47	42	42.6	41.8	42.2	42.0

[a] Mean values for the whole body of ten post-absorptive 60-day-old rats without intestinal lumen contents. Amino acids were analyzed as described by Li et al. (2011). Calculation were based on the molecular weights of intact AA

[b] Values for human fetuses (days 160–280 of gestation) and cattle (12 weeks old) were obtained from Davis et al. (1993). It was not reported whether calculations were based on the molecular weights of intact AA or AA residues. "–"denotes that data were not provided by the authors of the original studies

[c] Mean values for the whole body of six adult sheep (12-month-old) without intestinal lumen contents. Amino acids were analyzed as described by Li et al. (2011). Calculations were based on the molecular weights of intact AA

[d] Mean values for the whole body of ten post-absorptive 10-day-old chickens without intestinal lumen contents. Amino acids were analyzed as described by Li et al. (2011). Calculations were based on the molecular weights of intact AA

[e, f] Mean values for the whole body of ten post-absorptive 30-day-old pigs without intestinal lumen contents. Amino acids were analyzed as described by Li et al. (2011). [e]Calculations were based on the molecular weights of intact AA. [f]Calculations were based on the molecular weights of AA residues (molecular weight of intact AA-18)

and amounts of EAA) has been developed for poultry and swine (Baker 2009; Kim et al. 2001). The common features shared by these "ideal protein" models included (1) all protein EAA that are not synthesized by the animals; (2) several AA (cystine, glutamate, glycine, proline, and tyrosine) that are synthesized by animals to various extents; and (3) no data on alanine, aspartate, asparagine, glutamine, or serine. Because the content of proline plus hydroxyproline in the body was not determined, the relatively small amount of proline in the recommended ideal protein was only arbitrarily set and may limit maximal growth of animals. In contrast, very large amounts of glutamate (e.g., 13 times the lysine value) were used to presumably provide the entire need for "non-specific AA N". However, it was unknown whether glutamate fulfilled this role and whether excess glutamate might interfere with the transport, metabolism and utilization of other AA in the body. In light of the new notion on AA nutrition developed herein, we propose that the "ideal protein" include both EAA and NEAA in correct amounts and proportions (Fig. 2).

Conclusion

The traditional classification of AA as EAA or NEAA has major conceptual limitations in protein nutrition. It is unfortunate that dietary requirements of NEAA have not been recommended for animals and humans. However, emerging evidence shows that traditionally classified NEAA, particularly glutamine, glutamate, proline, and arginine, play important roles in regulating gene expression at both transcriptional and translational levels. There is also growing recognition that these NEAA participate in cell signaling via MTOR, AMPK, MAPK, and gases (NO, CO and H_2S). Exquisite integration of these regulatory networks has profound effects on cell proliferation, differentiation, metabolism, homeostasis, survival, and function. Thus, the classic concept of "the ideal protein" should include both EAA and NEAA to improve food efficiency, growth, and health of mammals (including humans), birds, and fish.

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Conflict of interest The authors declare that they have no conflict of interests.

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