Nutritionally Nonessential Amino Acids: A Misnomer in Nutritional Sciences[1,2]

Amino acids (AAs)[3] are organic compounds that contain amino and acid groups (1). Based on the configuration of glyceraldehyde (L- or D-isomers as introduced by Emil Fischer in 1908), AAs (except for Gly, taurine, β-alanine, and γ-aminobutyrate, which have no asymmetric carbon) exist as either L- or D-AAs. L-AAs are much more abundant than D-AAs in nature and are the physiologic isomers in animal and plant proteins. The AAs whose carbon skeletons are not synthesized de novo by animal cells were termed "nutritionally essential" AAs (EAAs) in 1912 and must be provided to animals to maintain their growth or nitrogen balance (2). In all animals, the EAAs consist of His, Ile, Leu, Lys, Met, Phe, Thr, Trp, and Val (3). In contrast, AAs whose carbon skeletons are synthesized de novo by animal cells were considered to be dispensable in diets and were classified as "nutritionally nonessential" AAs (NEAAs) (2). In most mammals (e.g., humans, rats, and pigs), the traditionally classified NEAAs are Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, Pro, Ser, and Tyr (3). The concepts of EAAs and NEAAs have been used for more than a century. Increasing evidence from studies in pigs, poultry, and fish has shown that animals do have dietary requirements of NEAAs to fulfill their genetic potential for maximum growth, reproduction, lactation, and production performance, as well as optimal health and well-being (4, 5).

Rates of NEAA synthesis depend on the availability of EAAs and glucose, as well as species, breed, age, physiologic status, and disease state. The de novo synthesis of Arg in animal cells is species specific, with most mammals (e.g., humans, pigs, cattle, sheep, mice, and rats) synthesizing this AA from Glu, Gln, and Pro via the intestinal-renal axis. However, birds and some mammals (e.g., cats and ferrets) cannot synthesize Arg from Glu, Gln, or Pro in the enterocytes of the small intestine, which also may be true in most fish. In contrast to mammals, the synthesis of Pro from Arg in birds and certain fish is limited, and the synthesis of Pro from Glu and Gln is absent in birds and perhaps in most fish. The rate of Gly synthesis is much lower than the rate of Gly utilization in poultry and young pigs.

In addition to proteinogenic NEAAs, the de novo synthesis of nonproteinogenic AAs should also be considered in nutrition. In cats, the conversion of cysteine into taurine is limited due to a low activity of cysteine dioxygenase and of cysteine-sulfinate decarboxylase, which catalyzes the formation of taurine from cysteine-sulfinic acid. Human infants, who have relatively low activities of both cysteine dioxygenase and cysteine-sulfinate decarboxylase compared with adults, require the dietary intake of taurine for maintaining normal retinal, cardiac, and skeletal functions. Pigs, ruminants, and poultry do not need dietary taurine for growth, milk production, or egg production. The supplementation of taurine to all plant–protein, taurine-free basal diets enhances growth and feed efficiency in carnivore fish (e.g., the rainbow trout and the Japanese flounder), but not the common carp, which suggests the suboptimal de novo synthesis of taurine by certain aquatic species (6).

In nonruminants, the nutritionally important sources for the carbon skeletons of NEAAs consist of glucose and EAAs, whereas EAAs, but not ammonia, are nutritionally relevant sources of the α-amino group of NEAAs (1). In support of this view, the addition of safe amounts of ammonium chloride to the diets of nonruminants (e.g., rats, pigs, and poultry) does not result in the production of a nutritionally important quantity of any AA (7). Exogenous or endogenous ammonia is converted preferentially into urea in nonruminant mammals or into uric acid in birds (1). In the rumen of ruminants, a physiologic amount of ammonia is utilized by bacteria to form all AAs in the presence of adequate carbohydrates and sulfur; and the AAs are utilized by microbes for the synthesis of proteins, which are digested in the abomasum and small intestine. The pathways for ruminal ammonia assimilation are important in ruminants that consume low-quality feedstuffs (e.g., roughages and forages) and recycle urea through the saliva and blood circulation. Although ammonia is also converted into AAs by the bacteria in the large intestine, the nutritional importance of these reactions for AA syntheses is limited for animals (1). This is because the resulting AAs are primarily converted into microbial proteins in the hindgut, where proteins are not absorbed into the epithelial cells and are excreted in the feces.

Although protein biosynthesis requires all proteinogenic AAs, NEAAs confer many functions that cannot be fulfilled by EAAs (1). These functions include the following: neurotransmission (Glu and Gly); the renal regulation of acid-base balance (Gln); the conjugation with bile acids (Gly and taurine); antioxidative reactions in retinal cells, heart, and skeletal muscle (taurine); the conversion of folate to tetrahydrofolate in one-carbon metabolism (Ser and Gly); syntheses of aminosugars (Gln), nucleotides (Asp, Gln, and Gly), glutathione (Glu, Gly, and Cys), heme

[3]Abbreviations used: AA, amino acid; AASA, amino acid that is synthesizable de novo in animal cells; EAA, nutritionally essential amino acid; mTOR, mechanistic target of rapamycin; NEAA, nutritionally nonessential amino acid.

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(Gly), NO (Arg), choline (Ser), carnitine (Ser), creatine (Arg and Gly), γ-aminobutyrate (Glu), dopamine (Tyr), melanin (Tyr), thyroid hormones (Tyr), polyamines (Arg and Pro), D-Ser (Ser), and D-Asp (Asp); and low-molecular-weight substances (e.g., NO, carbon monoxide, hydrogen sulfide, polyamines, creatine, serotonin, dopamine, agmatine, melanin, and melatonin). In addition, some NEAAs (e.g., Arg, Glu, Gln, and Gly) can activate cell signaling pathways, such as the mechanistic target of rapamycin (mTOR) and MAPK. NEAAs are more abundant than EAAs in the bodies of animals, such as pigs, cattle, sheep, chickens, rats, and humans, as well as in skeletal muscle, milk, and eggs. Thus, the needs for NEAAs for growth, lactation, and egg production are greater than those for EAAs.

A careful review of the literature has revealed the lack of experimental evidence for the sufficient synthesis of all NEAAs in animals (4, 5). Rather, extensive studies indicate that animals and humans cannot adequately synthesize NEAAs to meet optimal metabolic and functional needs under either normal or stress conditions. The AAs that are synthesizable de novo in animal cells (AASAs) should not be classified as NEAAs. Thus, the term "NEAAs" is a misnomer in nutritional sciences and should no longer be used. All proteinogenic AAs and certain nonproteinogenic AAs (e.g., taurine) should be considered to be essential nutrients in the diets of animals and humans.

Deficiencies

Deficiencies of NEAAs in animals and humans cannot be as readily detected as those of EAAs. Nonetheless, the inadequate intake of dietary NEAAs can result in deficiencies in the body. This notion is supported by many lines of evidence (4, 5). First, providing an Arg-deficient diet to men for 9 d decreased both the number and motility of sperm cells by 90%. Similarly, a deficiency of dietary Arg in young male rats over a period of 2 mo resulted in progressive damage to the testes, the absence of sperm production, and the filling of the lumina of the tubules with cellular debris, leukocytes, and macrophages. Second, endogenous synthesis of Gly in human infants and young pigs can satisfy, at most, only 50% of the metabolic needs for maximum protein synthesis. Third, young or adult humans cannot synthesize a sufficient quantity of Pro to repair wound tissues, whereas preterm infants cannot synthesize enough Gln or taurine. Fourth, the lack of some NEAAs in chicken and rat diets (e.g., Glu and Gln) precludes their maximum growth. Similar results have also been reported for various species of fish. Fifth, in weanling pigs fed diets containing the same amount of EAAs, a reduction in the dietary intake of NEAAs limited tissue protein synthesis and growth performance. Sixth, diets must contain sufficient amounts of *1*) Arg and Gln to support optimal fetal, neonatal, and postweaning growth in pigs; *2*) Pro, Glu, and Gly to sustain maximal growth performance and feed efficiency in early-weaned pigs; and *3*) Arg, Gln, and Glu to maximize milk production by lactating sows. Likewise, gestating ewes cannot sufficiently synthesize Arg or Gln to support maximum fetal growth. Furthermore, lactating cows do not produce adequate NEAAs to maximize milk production, because the abomasal infusion of 300 g Gln/d or an intraduodenal infusion of 80 g Pro/d into lactating cows increased milk protein yield. Therefore, deficiencies of NEAAs result in embryonic deaths, fetal growth restriction, impaired immune response, neurologic disorders, and increased risk of metabolic and infectious diseases, as well as suboptimal postnatal growth, lactation, and efficiency in nutrient utilization.

Dietary Recommendations

The current DRIs do not provide values for dietary requirements of NEAAs for infants, children, or adults. In 2016, dietary requirements of NEAAs were recommended by researchers for healthy infants, children, and adults (grams per kilogram of body weight per day)—for example, Arg: 71.3, 52.3, and 47.5 g · kg body weight^{-1} · d^{-1}, respectively; Gln: 108, 79.2, and 72 g · kg body weight^{-1} · d^{-1}, respectively; and Gly: 76.7, 56.2 and 51.1 g · kg body weight^{-1} · d^{-1}, respectively (8). In 2012, the NRC (9) recommended dietary intakes of digestible Arg (percentage of diet; as-fed basis) for swine at all production stages: 5-kg pigs, 0.75%; 10-kg pigs, 0.68%; 20-kg pigs, 0.62%; 100-kg pigs, 0.38%; gestating dams, 0.36% (days 0–90), 0.47% (days 90–114); and lactating sows, 0.60% (parity 1) and 0.54% (parity 2).

Food Sources

All fresh plant- and animal-source foods provide protein-bound NEAAs and, to a much less extent, free NEAAs (1). Processed foods contain protein-bound NEAAs but less free NEAAs than fresh foods. The content of NEAAs varies greatly among foods. Milk is an abundant source of free Glu and Gln (1 and 4 mmol/L, respectively, in sow milk) and contains ~10% Glu and 10% Gln in its proteins (gram per gram). Watermelon juice is rich in Arg and its immediate precursor L-citrulline (1.2 and 2.0 g/L, respectively). The total amounts of Arg, Glu, Gln, Gly, and Pro in beef cuts are 5.04, 7.26, 4.84, 3.27, and 3.32 g/100 g dry weight (9). Compared with plant-source foods, animal-source foods generally contain more Gly and Pro plus hydroxyproline per gram of protein.

Clinical Uses

NEAAs are effective at improving animal and human health (1). The oral administration of Ala has long been used to treat subjects with muscular atrophy. In addition, patients with an inherited inability to synthesize AAs, such as Arg, Asn, Gln, Ser, and Gly, are supplemented with these AAs in enteral or parenteral diets. Furthermore, Arg and Gln are used to enhance skeletal muscle mass and function in muscle builders, whereas Arg is taken orally to augment the synthesis of NO (the major vasodilator and an inhibitor of platelet adhesion to blood vessel walls) and to improve fertility in men. Finally, Gly is used to prevent and treat diarrhea in calves, whereas monosodium Glu is added as a flavor to food to stimulate appetite in the elderly.

Toxicity

Little information is available with regard to the toxicity of excess NEAAs in animals or humans. The DRIs do not provide data on the Tolerable Upper Intake Levels of dietary NEAA intakes by infants, children, or adults (10). When intakes are equally divided in 3 different meals, a 70-kg healthy adult can tolerate 50 g Gln/d and ≥20 g Arg/d (11). Increasing the intakes of all NEAAs by up to 100% beyond those from basal diets is safe for pigs, poultry, ruminants, and fish, except for possibly during the periconception period. Nonpregnant pigs fed a corn- and soybean meal–based diet containing 16–20% crude protein can tolerate dietary supplementation with 1% Gln, 2% Arg, 2% Pro, 2% Gly, 2% Ala, and 4% monosodium Glu (12). Pregnant gilts and sows fed a corn- and soybean meal–based diet containing 12% crude protein can also tolerate dietary supplementation with 1% Arg between days 14 and 25 or between days 14 and 114 of gestation and with 1% Gln between days 90 and 114 of gestation, as can lactating sows between days 1 and 21 postpartum (12). However, dietary supplementation with 0.83% Arg between days 0 and 25 of gestation reduces progesterone production and embryonic survival in gilts (13).

Recent Research

There is growing recognition that the traditional term "NEAAs" has conceptual limitations in nutrition (4, 5) and should be replaced by the new term "AASAs." Research is currently being conducted worldwide to define the optimum dietary requirements of AASAs by livestock (e.g., pigs, cattle, sheep, and goats), poultry, aquatic animals (e.g., fish and shrimp), and companion animals in their life cycles and in response to physiologic, pathologic, and environmental changes (1, 5, 14). Criteria for assessing the dietary requirements of AASAs include embryonic survival and litter size, fetal growth, milk production, postnatal growth, skeletal muscle gain, reduction in white adipose tissue, digestive function and intestinal integrity, immunity and health status, feed efficiency, and meat quality (4, 5). Moreover, the long-standing "ideal protein" concept, which concerns only EAAs, is now being revised for nonruminants by the inclusion of AASAs. The establishment and adoption of new data on dietary requirements for AASAs represent a new paradigm shift in protein nutrition. This line of research has important implications for sustaining animal agriculture (including aquaculture), as well as for improving the growth and health of animals and humans.

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