Lysine, Arginine, and Related Amino Acids: An Introduction to the 6th Amino Acid Assessment Workshop

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Abstract
The focus of the 6th workshop is on lysine, arginine, and related amino acids. Functions, metabolic pathways, clinical uses, and upper tolerance intakes are emphasized in the articles that follow. Lysine is arguably the most deficient amino acid in the food supply of countries where poverty exists, and since the discovery of the nitric oxide synthase pathway, arginine has come into prominence clinically because of the role of nitric oxide in cardiovascular physiology and pathophysiology.

Credit must be given to the late Vernon Young for having the vision to organize and obtain support for the International Council of Amino Acid Science (ICAAS), which began in 2001 with the 1st meeting held in Tokyo. The idea behind ICAAS was to assemble a critical mass of expert scientists who could present research findings and engage in fruitful discussion of the particular topic to be emphasized at each individual conference. The first 3 conferences focused on general questions and problems dealing with function, upper limits, and biomarkers. Beginning with the 4th conference in Kobe, Japan, more specific groups of amino acids were emphasized. Thus, branched-chain amino acids (1) were the topic for discussion at the Kobe meeting, and sulfur amino acids were the focus of the 5th ICAAS conference in Los Angeles (2,3). The basic amino acids, arginine and lysine, are emphasized in this, the 6th ICAAS Workshop held in Budapest, Hungary.

Arginine
The articles that follow discuss functions, metabolism, pharmacokinetics, and clinical uses for supplemental arginine. Clearly, urea-cycle function and nitrogen elimination are crucial features in the functionality of arginine. Interspecies comparisons in the consequences of arginine deficiency are fascinating (4,5).

Feline species have very limited capacity to make citrulline in intestinal mucosal cells, and as a result, cats consuming only 1 meal of an arginine-free diet develop severe hyperammonemia and often die after only 24 h (5). In contrast, feeding chicks (zero in vivo arginine biosynthesis) an arginine-free diet, although resulting in negative growth, yields mortality only after 27 d of feeding (6). Young pigs do not grow optimally when fed a diet very low in arginine (7,8), but adult pigs, including gravid females, synthesize enough arginine (in kidney tissue) to meet their functional requirements (9,10). A classic study was done at UC-Davis in which an arginine-free diet was consumed by adult humans for 5 d (11). No symptoms of arginine deficiency occurred, and plasma ammonia and urinary orotic acid remained in the normal range. The results of this study suggest that normal healthy adults can synthesize enough arginine to meet minimal functional requirements.

Ball’s laboratory in Alberta fed (using a gastric catheter) or provided IV an arginine- and proline-free diet to neonatal piglets (12). Whether they were fed enterally or parenterally, hyperammonemia rapidly occurred. However, providing proline in the arginine-free formula prevented the elevation of plasma ammonia, but only in the case of enterally fed piglets. These interesting findings demonstrate that the gut is vitally involved in the arginine-sparing effect of proline (13).

Antagonism of arginine by excess dietary lysine is of great interest in animal nutrition. Species differences exist in that antagonism occurs in chicks (14), rats (15), guinea pigs (16), and dogs (17) but not in pigs (18). This is of greatest practical significance in avian species because they have high arginine requirements, and excess lysine enhances arginine catabolism by inducing kidney arginase.

Arginine has become a prominent amino acid in several disease states, not only those related to nitric oxide (NO) production but also those associated with the arginine catabolic enzyme,
arginase (19–21). Arginase is released from human red blood cells and is therefore a factor in hemolytic diseases such as sickle cell disease. Arginase activity is also elevated in asthmatic patients, possibly limiting the availability of arginine for NO biosynthesis. These topics are discussed in more detail in the articles that follow.

**Lysine**

Lysine could be viewed as the “forgotten” amino acid in human nutrition. This amino acid is rich in the food supply of developed countries. However, in poor countries where cereals dominate the food supply, lysine is the most limiting amino acid in the food supply. Based on rat studies, every cereal grain that has been studied is not only deficient but also 1st limiting in lysine (22). Lysine is also the most limiting amino acid in typical diets fed to pigs; it is second limiting after methionine in typical diets fed to avian species. Not surprisingly, therefore, well over 90% of the total lysine production is used to supplement animal diets. In 2005, 200,000 metric tons of lysine were used in the United States, alone, for animal feed applications (23). Thus, lysine has probably been studied more in animal nutrition than any other amino acid, but it has not received the same degree of emphasis in human nutrition. This is perhaps because few pharmacologic uses for lysine in the clinical setting have been advanced.

Topics dealt with in the articles that follow are 1) lysine metabolism and mitochondrial uptake (24, 25), 2) susceptibility of lysine in both its free and protein-bound state to Maillard browning in foods and feeds exposed to high temperature and humidity (25,26), 3) susceptibility of lysine in foods under heat and alkaline conditions to loss of bioactivity as a result of lysinoalanine synthesis (27, 4) upper limit studies, including effects of lysine per se as well as effects of the HCl portion of lysine administered as lysine HCl (18,28–31), 5) antagonism of arginine caused by excess lysine inducing kidney arginase in avian species (14,32), 6) use of lysine as a reference amino acid in diet formulation for animals based on the “ideal protein” (i.e., ideal amino acid ratios) concept (5,33–37), and 7) molecular genetic approaches to increasing the lysine content (both free and protein bound) in cereal grains and oil seeds (38,39).

In the articles that are included in this supplement, topics ancillary to but associated with lysine and arginine are discussed as well. These include metabolites of lysine such as saccharo-pine, α-aminoacidic acid, α-ketoacidic acid (also a metabolite of tryptophan), trimethyllysine, and carnitine as well as metabolites of arginine such as ornithine, citrulline, dimethylarginine, creatine, agmatine, polyamines, urea, and, of course, NO.

**Literature Cited**