Introduction to the 3rd Amino Acid Assessment Workshop\textsuperscript{1}

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ABSTRACT A series of Amino Acid Assessment Workshops (AAAWs) are being organized and conducted to bring together experts in amino acid nutrition, metabolism, cell and molecular biology, toxicology, and regulation/policy with the eventual goal to establish a paradigm for the characterization of risks associated with ingestion of specific intakes of amino acids by humans. In this brief introductory article, I present the rationale behind these AAAWs, which basically emerges from the fact that there is little systematic information about the adverse effects and the pathophysiological mechanisms of excessive intakes of single amino acids or of mixtures of amino acids in human subjects. This 3rd AAAW extends, as well as builds upon, the information collected at the 1st and 2nd AAAWs. The previous two workshops focused attention largely on the metabolism, mechanism of action, and functions of amino acids. This 3rd AAAW will focus particular attention on intakes needed to meet physiological requirements and above, host and diet factors that affect these needs and responses, as well as variation in responses to and levels of intake of amino acids among individuals. In this context, the overall objective is to establish the science and knowledge base required for use in determining and/or predicting the upper level of the safe range of intake of specific amino acids under various host, agent (diet), and environmental conditions. J. Nutr. 134: 1555S–1557S, 2004.

KEY WORDS: • amino acid assessment workshop • AAAW • safe range • upper level • factors affecting response

Amino acids, a basic constituent of life, may have been delivered from extraterrestrial sources (1–3), triggering the appearance of life on Earth. In addition, they may have been spontaneously generated under the reducing atmosphere of primitive Earth and/or, according to one general theory, they may have emerged in a pressurized iron-sulfur world involving an environment of iron-sulfide and hot magnetic exhalations (4,5). The subsequent course of evolution involved the appearance of the RNA world (6,7) and later those of the DNA and protein worlds along with the elaboration of genetically directed protein synthesis machinery. In higher mammals this mechanism selects for those amino acids along with the elaboration of genetically directly polypeptide chains. These may then associate with other polypeptides and/or undergo post-translational modification and folding into their functional forms. It is these amino acids that quantitatively make the major contribution to the amino acid economy of the mammalian organism, including humans and, in turn, dictate the nutritional needs and status of the host.

Not all of the amino acids are nutritionally equivalent; some can be synthesized de novo at rates adequate to meet metabolic needs (dispensable amino acids; e.g., alanine, serine) whereas others (indispensable amino acids; e.g., lysine, tryptophan) cannot be synthesized at all. Yet for some others de novo synthesis occurs but at a rate insufficient to meet metabolic condition under a specific certain pathophysiological state (conditionally indispensable amino acids; e.g., cysteine, arginine) (8), such as trauma, prematurity, and rapid catch-up growth. Furthermore, the proportions of amino acids in human diets differ from those required to support efficiently the process of polypeptide synthesis, which is necessary for survival, maintenance, and growth of the individual. However, these differences are usually of little importance in terms of body amino acid and nitrogen (protein) homeostasis. Nevertheless, inadequate or excessive amounts of total amino acids (protein) or of individual amino acids (indispensable or conditionally indispensable) result in unfavorable effects. Indeed, as discussed elsewhere (9), amino acid metabolism provides a good example of an interorgan process in which events in different tissues combine and collaborate to bring about overall physiological phenotype. This collaboration includes a maintenance of concentrations of amino acids circulating in the blood, normally within certain limits, and via specific transport systems (10); this ensures a supply of these substrates for protein synthesis throughout the tissues and organs of the body. The individual organs make unique contributions to the metabolism of the various amino acids; the earlier view of the role of the intestine in amino acid metabolism has been transformed from that of an organ that is only involved in digestion and absorption to one that obtains a substantial fraction of its metabolic energy from the catabolism of dietary amino acids and undertakes a significant metabolic processing of...
absorbed amino acids before their entry into the portal circulation (11). The liver is the major organ for the catabolism of amino acids and in the regulation of amino acid catabolism, therefore, plays a major role in determining dietary amino acid requirements. The fact that the rate of amino acid catabolism is never zero is one of the principal reasons why adults require a continuous supply of dietary nitrogen and indispensable and conditionally indispensable amino acids.

A challenge in human nutrition is to define the range of individual amino acid intake, from a low to a high level, within which amino acid and nitrogen homeostasis is effectively maintained. In particular, it is necessary to determine the functional consequences of intakes that fall, both, only just outside or well outside of this “homeostatic” range and how to best predict such effects under various dietary, host, and environmental conditions.

Food proteins normally provide for our nitrogen and amino acid needs but free amino acids/mixtures/peptides are used in clinical nutrition and for health promotion. Under these latter conditions, such as in the performance arena, possibly in the dependent elderly and/or those who receive supplements in disease states is where the risk of excessive amino acid intakes may be more common. Furthermore, an excessive intake may arise due to human error (12) and if the pathophysiology of the high amino acid intake is understood it might be possible to develop approaches for effective treatment of individuals affected. Hence, to assure their safe and effective application, it is necessary to establish a sound, scientific basis for evaluating their efficacy and “safety.” In this context a series of questions immediately emerge: i) what are the functions and mechanisms of action of the individual amino acids; ii) what are the adverse effects of excessive intakes and what are the mechanisms involved; iii) how might these untoward effects be best predicted; iv) what is the effect of genetic and of other factors on the response to amino acid intakes; and v) what are the critical research issues?

To meet this challenge and, as described earlier (13), a series of workshops was planned and initiated under the auspices of the International Council on Amino Acid Science (ICCAS; esato@icaas-0rg.com), with its secretariat located in Tokyo, Japan, to address these major issues.

The 1st AAAW

The 1st AAAW was held in Tokyo in June, 2001. The purpose of this AAAW was: i) to review the roles and metabolism of dietary amino acids in relation to cell and organ function and ii) to identify the possible consequences associated with abnormal or unusual, in particular, high, intakes in human subjects. The focus of the discussions was intended to be, as far as possible, on mechanisms and quantification. It was planned that a working framework for assessment of the consequences of abnormal amino acid intakes might be developed, together with a number of the details of a research program required to generate a sufficient knowledge base for purposes of making sound and effective recommendations and policies.

The 2nd AAAW

The 2nd AAAW was held in Hawaii in October, 2002, and the major focus of this workshop was on how recent advances in biology made somewhat before and during this genome-sequencing era (and the associated technology) might help to better understand the mechanisms involved and improve the ability to predict the responses of individuals to altered intakes of amino acids and their safety. Some of the issues of interest in anticipation in this workshop were: i) to determine how to define and identify molecular signatures of a pathological response to amino acid intake; ii) to see if we can identify a distinct set of genes that differentiate adequacy from excess for specific amino acids; iii) to explore the power of a microarray approach to establish a molecular profile of amino acid adequacy/excess; and iv) to decide on which organs/tissues to focus a major effort with respect to assessing the pathophysiological consequences and mechanisms of excessive intakes. Should it be the brain, the liver and/or the gut, for example, and how might the effects in such organs be probed in a noninvasive way?

Finally, regulation, and in consequence disregulation, can occur at various loci downstream from the genome, including the proteome, metabolome, and the integrated system in which the different parts of the system (genes, proteins, metabolites) operate. Each of these levels should be considered in reference to the issues above and together it was thought that these “omic” categories and their enabling technology should open up new lines of investigation making it possible to move from use of “simple/single” indicators (markers) of adequacy/deficiency/excess to new and more comprehensive indices of functional significance, as previously discussed (13).

Although not all of the issues identified above were adequately discussed and/or resolved at this 2nd AAAW, in the aggregate it helped to point out a potential route for better understanding and predicting the responses to altered amino acid intakes and their safety. The interested reader is encouraged to consult The Journal of Nutrition web site (www.nutrition.org) for access to the full proceedings of the 2nd AAAW.

The 3rd AAAW

The first two AAAWs, as noted above, focused attention largely on metabolism of amino acids, their mechanism(s) of action, and the function of amino acids. For this workshop we focus more attention on intakes to meet physiological needs, the host and dietary factors that affect these needs and the nature of the host response, variation in responses to and levels of intake of amino acids among individuals in populations. All of this is to be viewed with an eye as to how the upper level of the safe range may be determined/set. It is recognized that this will require an approach that differs from that established for nonnutrients, which is based on hazard identification, hazard characterization, exposure assessment, and risk characterization (14–18), involving a dose-response assessment to define levels of intake without appreciable adverse effects. However, it is clear from the recent initiative by the U.S. Food and Nutrition Board/Institute of Medicine (FNB/IOM), which was to set new dietary reference intakes including tolerable upper levels (ULs) (19), that application of the approach used for nonnutrients would be unworkable for nutrients, including amino acids.

Coda

Again, as stated earlier (13), we have much to learn about the metabolic and functional consequences of specific and especially relatively high intakes of amino acids in human subjects under varying physiological conditions. We anticipate that with this continuing series of AAAWs it will eventually be possible to provide a sound scientific basis for maximizing the contribution that amino acid intake(s) makes to health promotion and for attenuating disease.
LITERATURE CITED


