# "Amino Acids in the 21st Century" (5) –ARGININE IN DISEASE–

Previous articles in this series provided basic information regarding the synthesis of arginine and nitric oxide (NO) (Amino Acids Link News, Vol. 8, October 2004) and the urea cycle, arginine synthesis, and usual arginine requirements (Amino Acids Link News, Vol. 9, January 2005). This article will briefly consider diseases in which changes in levels of arginine and its metabolism have been implicated in the disease process. However, the reader should appreciate that this is a very large topic, and only a few points can be considered here. More detailed discussion can be found in the Proceedings of the Symposium on Arginine [1].

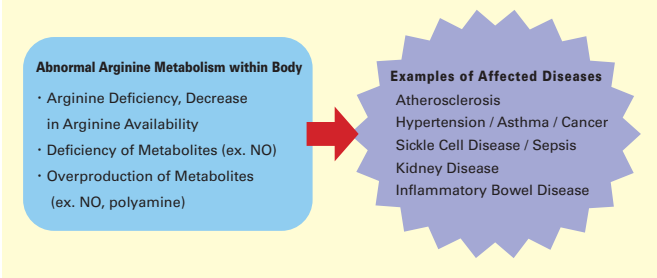
## Diseases with Abnormal Arginine Metabolism

Several examples of diseases in which levels of arginine or its metabolism have been associated with primary or secondary disease complications are listed in Figure 1. In cases where disruption of arginine metabolism has been identified, this generally involves one or more of the following: For example, (1) a deficiency or decreased availability of arginine within the body (example: sickle cell disease); (2) a deficiency of some key product of arginine metabolism such as NO (example: sickle cell disease); and (3) overproduction of some product of arginine metabolism such as NO (example: sepsis) or polyamines (example: some cancers). None of the diseases listed causes the overproduction of arginine within the body. It is important to note that either too little or too much of some arginine-derived compounds such as NO can be unhealthy and even life-threatening. This important fact emphasizes the need for careful studies to evaluate the consequences of arginine supplementation in specific diseases.

## Involvement with Cardiovascular Disease

Cardiovascular diseases represent a major health problem in much of the world, and a number of these diseases involve abnormal arginine metabolism. In many of these diseases the defect appears to be insufficiency of NO, which is derived from arginine. Examples include atherothrombosis, peripheral arterial disease, and hypertension. A key cell type that is affected in many diseases of the cardiovascular system is the endothelial cell. Endothelial cells, which form the inner lining of blood vessels, help to regulate blood pressure by producing NO from arginine. Insufficient NO production by endothelial cells may result from a number of underlying causes, many of which may potentially be treated by supplementation with arginine. Examples of such causes may be impaired cellular uptake of arginine from the circulation, inadequate levels of arginine in the circulation, decreased intracellular arginine levels due to elevated metabolism of arginine, and decreased synthesis of cofactors that are essential for function of the NO-producing enzyme nitric oxide synthase (NOS). Resent research has provided evidence that increasing availability of arginine can overcome some of these defects. In addition, arginine has antioxidant activity, can stimulate release of vasodilator compounds such as histamine, and can promote secretion of insulin that can enhance vasodilation. These properties may be beneficial for patients with cardiovascular disease. Although studies with humans that have been conducted to date have not yet provided clear-cut results for specific cardiovascular diseases (perhaps due to complexities of human physiology and biochemistry which we do not yet fully understand), results in some cases have been encouraging, indicating that additional well-planned studies should be performed.

Figure 1: DISEASES WITH ABNORMAL ARGININE METABOLISM




## Involvement with Cancer

Cancer is another major type of disease in which abnormal arginine levels or arginine metabolism can contribute to the disease process. Unfortunately, it is not possible to make a general statement about the roles of arginine in cancer because of the fact that many different types of cancer exist and the different types vary widely in their metabolism of arginine. The ability of some types of tumors to develop and progress may depend on an increased capacity for using arginine for synthesis of NO, which can promote formation of blood vessels to supply the tumor with nutrients, or polyamines, which are compounds that are required for cell division. Consequently, increasing arginine levels by dietary supplementation may promote growth of some types of tumors but may have no effect on growth of other types. It is important to note that there is no evidence that arginine supplementation increases the incidence of cancer. A recent study identified arginine deficiency in patients with renal cell carcinoma. These patients had circulating levels of arginine that were approximately half of normal levels, and these low levels were associated with impaired function of immune cells. Further studies will determine whether arginine supplementation for these patients will improve immune function without promoting tumor growth.

## Involvement with Asthma

Asthma is a widespread lung disorder that not only restricts physical activity but also can be life-threatening. Recent studies have found increased expression of arginase in lungs of asthma patients and in animal models of asthma, as well as reduced levels of arginine in the blood of patients experiencing an acute asthma attack. The consequences of these changes have not been completely defined but it appears that they may play a role in the difficulty in breathing during an acute asthma attack, as well as in long term changes in the lung in chronic asthma. There is now considerable interest in understanding how to modify arginine metabolism in order to develop new asthma therapies.

## Involvement with Sickle Cell Disease

It is now recognized that patients with sickle cell disease, which is an inherited disease caused by a specific mutation in the hemoglobin molecule, also have a chronic arginine deficiency that contributes to the serious secondary complications of this disease. The circulating levels of arginine in healthy adults after an overnight fast range from 80 to 120 micromolar. However, circulating arginine levels in sickle cell patients are approximately half of normal values, and low arginine levels have recently been found to be associated with pulmonary hypertension and increased risk of death [2]. Although this new information suggests that dietary supplementation with arginine may improve the health of these patients, clinical nutrition studies must be carried out to evaluate whether long-term dietary supplementation with arginine---or its precursor citrulline—will be beneficial and without risk of deleterious side effects.

## Benefit of Arginine Supplementation

Arginine, either alone or in combination with other nutrients such as glutamine, certain fatty acids and nucleotides, has been used as a supplement to enhance function of the immune system, particularly in patients who are recovering from traumatic injury or surgery. In theory, this is likely to be beneficial, based on our current knowledge of the roles of arginine metabolism and how it is disrupted in specific diseases. However, reviews of a large number of clinical studies suggest that it is difficult to draw general conclusions as to the benefit of arginine supplementation in enhancing immune function of patients. This is due to the fact that various investigators have studied different diseases, used different doses of arginine, with or without other nutritional supplements, administered the diets for different lengths of time in different studies, or included too few patients in their study to allow definite recommendations to be made. Taking into account these limitations of the studies, it nevertheless appears that arginine supplementation may be beneficial for patients without infectious disease who are arginine-deficient. Therefore, it should be kept in mind that recommendations for individual patients should always be based on thorough evaluation of their overall clinical condition.

There are several possible ways for achieving arginine supplementation, and a single mechanism of supplementation may not be appropriate for all diseases. The simplest method is simply dietary supplementation with arginine, which is known to be well-tolerated at amounts that are several times greater than the normal dietary intake. An alternative that is used clinically, particularly for patients who are unable to ingest orally, is parenteral infusion directly into the circulation. Of course, this approach should not be undertaken without medical supervision and thus would not be recommended for most individuals.
Another possibility is dietary supplementation with the amino acid citrulline, which is a precursor for synthesis of arginine within the body. There is relatively limited data for this mechanism in human studies, in part due to the fact that food-grade citrulline is more expensive than is food-grade arginine.
In summary, there are many diseases in which dietary supplementation with arginine—either alone or in combination with other nutrients—may prove to be beneficial. It is anticipated that further studies in this area will provide the information necessary to formulate new and effective nutritional guidelines that will improve patient health and quality of life.

1. Morris SM, Jr., Loscalzo J, Bier D and Souba WW (editors). Arginine metabolism: Enzymology, nutrition, and clinical significance. J. Nutrition, Vol. 134 (Supplement): 2741S-2897S, 2004.
2. Morris CR, Kato GJ, Poljakovic M, Wang X, Blackwelder WC, Sanchdev V, Hazen SL, Vichinsky EP, Morris SM, Jr., and Gladwin MT. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension and mortality in sickle cell disease. JAMA 294: 81-90, 2005.

### Dr. Sidney M. Morris, Profile

Dr. Sidney M. Morris, Jr., received his B.Sc. in Chemistry from the University of Texas at Austin and his Ph.D. in Biochemistry from the University of California at Berkeley. He performed postdoctoral work in the Department of Physiological Chemistry at the University of Wisconsin School of Medicine and in the Department of Pharmacology at Case Western Reserve University School of Medicine. Since 1983 he has been a faculty member at the University of Pittsburgh School of Medicine, where he is currently Professor of Molecular Genetics and Biochemistry. His research interests include metabolic and transcriptional responses to inflammation, with a major focus on the roles and regulation of arginine metabolism.

Please contact us:

**Ajinomoto Co., Inc., Amino Acids Department**
1-1, Suzuki-cho, Kawasaki-ku Kawasaki-shi, 210-8681, Japan Tel: +81 (44) 244-7107, Fax: +81 (44) 244-7135
E-mail: AA_PR@ajinomoto.com

**Ajinomoto AminoScience LLC**
4020 Ajinomoto Drive, Raleigh, NC 27610 Tel: 1-800-682-0982, Fax: 919-325-1420, E-mail: aminoacid-sales@ajiusa.com

**Europe**
**S.A. Ajinomoto OmniChem N.V.**
Industrial Research Park Fleming, B-1348 Louvain-la-Neuve, Belgium Tel: +32 (10) 48-3222, Fax: +32 (10) 45-6227
E-mail:amino@hbg.ajinomoto.com

**Shanghai Ajinomoto Amino Acid Co., Ltd.**
Rongle Dong Lu 518 Songjiang, Shanghai 201613, People's Republic of China Tel: +86 (21) 57743402, Fax: +86 (21) 57740433

Published by Amino Acid Department, Global Foods & Amino Acids Company, Ajinomoto Co., Inc.