

Newsletter Amino Acids Link News

Newsletter of Ajinomoto Co., Inc. Amino Acid Department

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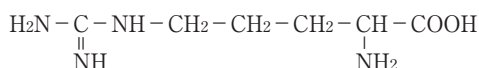


"Amino Acids in the 21st Century" ~Arginine as an Immune-boosting Nutrient~

Ajinomoto Co., Inc. is pursuing various researches under the premise "21st Century—The Century of Amino Acids." As part of a feature series entitled "Amino Acids in the 21st Century," in this edition we will introduce some applied research functions of amino acids. The first article covers arginine. Despite not being an essential amino acid, arginine is being lauded by many researchers because of its considerable effect on growth hormones as well as such crucial physiological processes in the endocrine system, the circulatory system and excretory system aiding ammonia detoxification. Moreover, since infants naturally synthesize so little of this amino acid, it is considered a semi-essential amino acid.

Properties of Arginine

● Chemical Composition:



● Crystal Structure : Rhombic system

● pH Level : Alkaline (pH 11—12)

● Taste : Bitter

● Properties : Highly water-soluble, but minimally soluble in ethanol

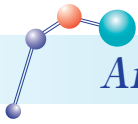
● Key Effects and Applications of Arginine

Effect	Application
① Maintains essential balance in infants	Additive in baby formula
② Stimulates the immune system	Immune-boosting nutrient; sports supplement
③ Activates hormones in the endocrine system (Growth hormones, insulin, etc.)	Diagnostic agent for endocrine system; sports supplement
④ Promotes vasodilation (Improvement of blood flow and alleviation of high blood pressure)	Antihypertensive agent; sport supplement
⑤ Promotes ammonia detoxification of the body	Fatigue-alleviating agent; treatment for hyperalaninemia; agent in improving kidney function; Sports supplement
⑥ Supports moisture retention	Cosmetics; haircare products
⑦ pH control as a strong alkaline	pH control agent; alkaline chemicals

● Crystal Magnification : (×100)



Arginine is gaining increasing attention recently for the important role it plays in immune function. Next we will explore the effect arginine has in boosting and regulating the immune system.



Mr.Fumio Ohta/AminoScience Laboratories

The Diverse Functions of Semi-essential Amino Acids

Although arginine is not an essential amino acid when maintaining nitrogen balance, it is considered as semi-essential amino acid that is required for normal growth. Moreover, since endogenous arginine synthesis may be limiting during illness, arginine is called conditionally essential amino acid. This unique amino acid is involved in numerous areas of physiological functions, including ammonia detoxification, secretion of certain hormones, endothelial function and immune modulation (table 1). The action of hormone secretion and ammonia detoxification are already put into practical use as medical supplies. In addition, the enteral nutritional products adapting the immunoregulation or other beneficial function of arginine also have been introduced into the marketplace. The major objective of this article is to review the recent studies concerning the role of arginine on immunonutrition and other supplemental use.

Table 1 Physiological Functions of Arginine

Circulatory System	Endocrine System	Other
Contraction of smooth muscle cells ↑	Insulin secretion ↑	Urea cycle activation ↑
Proliferation of vascular endothelial cells ↑	Growth hormone secretion ↑	Insulin sensitivity ↑
Release of endothelin-1 ↓	Glucagon secretion ↑	Ammonia detoxification ↑
Adhesiveness of white blood cells ↓	Prolactin secretion ↑	
Concentration of platelets ↓	Creatine production ↑	
Production of hydrogen peroxide ↓	Proline production ↑	
	Polyamine production ↑	

Mechanism as Immunonutrient

Immunonutrition can be defined as the enteral nutrient that is fortified the specific nutrient for the purpose of enhancing and/or modulating immune system. This enteral nutrition is applied to the patient in the intensive care unit, elective surgery, or critically ill patient with severe burns. The aims of immunonutrition are mainly to improve the outcome or to reduce the length of hospital stay. The nutrients most often used in immunonutrition are arginine, glutamine, branched chain amino acids, n-3 polyunsaturated fatty acids, and nucleotides (table 2). Commercially available enteral diets, however, contain

the combination of these nutrients and individual components have been reported to preserve or augment various immune functions, arginine is the basic component of virtually all the immunonutrition.

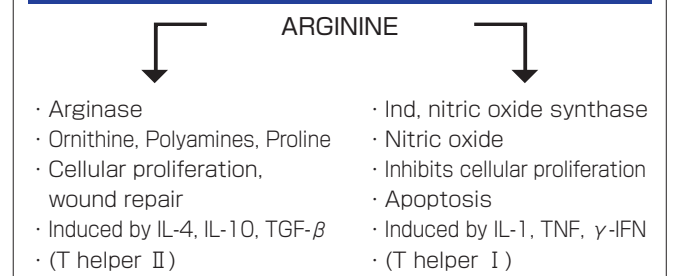
Table 2 Immunonutrients

		Conceivable mechanism
Amino acids	Glutamine, Arginine	Energy source of immune cells, nitric oxide precursor
Lipids	ω n3-polyunsaturated fatty acids	Suppression of inflammation
Nucleotides	RNA	Bolstering of immune cell function
Vitamins	Vitamin E, Vitamin C	Antioxidation function
Other	Fiber	

In experimental models and in the clinical setting, the administration of arginine improved immune response such as bacterial clearance, T-cell function, and cellular production of cytokines; this protective effect was reversed when nitric oxide inhibitors were administered. Moreover, the synthesis of nitric oxide from arginine may be responsible for the vasodilator tone, suppression of cell proliferation and the increased visceral microperfusion.

Thus, the immune enhancing function of arginine and the effect of immune argumentation and suppression thorough arginine-nitric oxide pathway have been advocated as potential mechanisms of immunonutrient. Some reports showed the elevated arginine metabolism, upregulation of arginase activity in wound-derived fibroblasts and elevated concentrations of citrulline and nitrite in wound fluid. Such circumstantial evidence may indicate the elevated arginine demand in stressed tissues or organs (figure 1) . Although these hypotheses on the mechanism of arginine as remain to be proven, the enhancement and modulation of the immune and inflammatory responses seem important role of arginine as an immunonutrient.

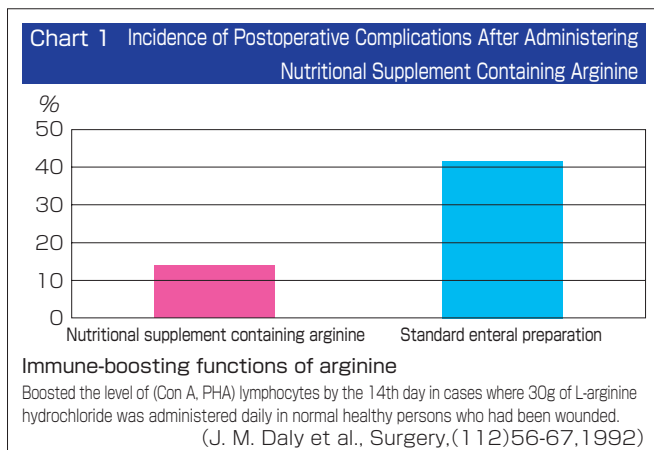
Figure 1 Functions of Arginine



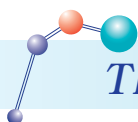
(How do Immune enhancing diets work?
Juan B. Ochoa, University of Pittsburgh 2003 Nutritionweek)

Attention-Getting Study for Supplement Use

Arginine or immunonutrition containing arginine has been applied to various conditions of the patient, and data on susceptible condition is reported. Recent large randomized, double-blind clinical studies showed that the preoperative administration of arginine and other immunonutrients in patients with gastrointestinal cancer significantly reduced the incidence of postoperative complications and length of hospital stay (chart 1).



Moreover, many examinations for chronic heart failure and healthy people other than critically ill patients were also performed. These studies have shown improved aerobic capacity in chronic heart failure, and marked elevation in plasma cortisol and hGH levels during or after the exercise of healthy men. Another study offers the possibility of arginine induced reduction in postexercise carbohydrate oxidation rate; which suggests the increased availability of glucose for muscle glycogen storage.



The Ever-increasing Importance of Arginine in the Medical Setting

Research has proceeded from early times on the clinical functions of arginine in the field of nutritional immunology. I would now like to call on Professor Hideaki Saito, who has been leading the research of nutritional immunology for many years and been involved in the actual development of nutritional immunological products, to answer some questions for us.

Nutritional Management Helps to Boost Patient Immune Function

Q.1 While active in the forefront of surgery, Dr. Saito has also been researching in depth patient immune function. Would you please tell us why you began this research?

A.1 One of the most frequent complications of trauma, burns, injuries and major surgery is severe

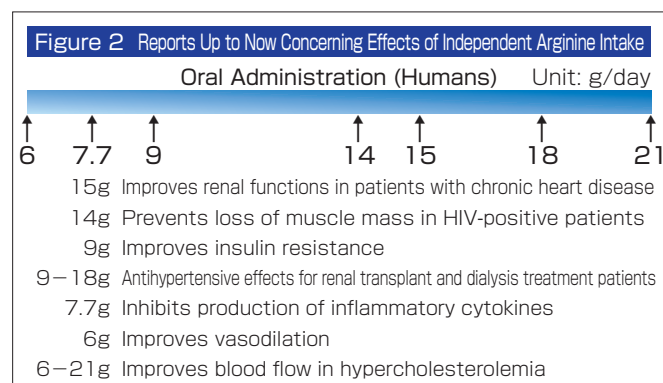
infection. Once severe infection occurs it can progress to multiple organ failure, resulting in poor prognosis. Nutritional management is one of the fundamental treatments in such severe illness. In severe illness the body's defense mechanisms and immune functions are impaired, leading to the onset and aggravation of infection. It has also become clear that the body's defense mechanisms and immune functions are closely related to the nutritional state. It has therefore now been thought that severely ill patients require some sort of new nutritional methods for preventing and treating infection by enhancing and modifying immune function.

Research was thus begun on the body's defense mechanisms and immune functions in severely ill patients. Investigations were also begun on the effects of nutritional management on immune functions.

These findings may have importance for considering new uses of arginine as nutritional supplements.

It is also known that in certain conditions that arginine immunonutrition failed in creating the expected effect. Various clinical studies are being continued, and proper usages of immunonutrition will be further clarified through such efforts.

Immunonutrition is the new nutritional approach that emphasizes the function of each specific nutrient. Among all immunonutrients, arginine takes significant lead in enhancing and modulating action; it is expected that arginine will continue to contribute to various uses of clinical nutrition and supplementation in the future. (figure 2)



Profile of Fumio Ohta

Graduated from the Animal Medicine, University of Tokyo, and entered Ajinomoto Co., Inc. in 1996. Had engaged in a development of diabetic drug in Pharmaceutical Research Laboratory of for 5 years. Belong to AminoScience Laboratory since 2001. Animal doctor.

Q.2 What are the most severe effects on immunity in patients during the preoperative and postoperative periods?

A.2 Factors that influence postoperative immune functions include preoperative concurrent pathologies, the extent of the surgery, bacterial contamination during surgery, and blood transfusions. If the surgery is to the same extent, preoperative concurrent pathologies have a major effect on postoperative immune function. Preoperative concurrent pathologies which have deleterious effects include malnutrition, diabetes mellitus, and liver disease. Use of immunosuppressive drugs, such as steroids also depresses the immune function.

In particular, malnutrition is seen in about 20 to 30 percent of all in-hospital patients regardless of whether they have been admitted to the surgical department or internal medicine department. When oral medication is restricted due to certain diseases, the intake of both calories and proteins decrease. The complement system, phagocyte system, and T-cell system are involved in the body's defense against infection, but when the intake of calories and proteins is restricted at the same time, all of these defense factors are impaired. However, it is known that even when the same calories or nutritional components are administered, the route of nutritional support, enteral or parenteral, may influence host defense mechanisms. Furthermore, it has also become clear that specific nutrients such as arginine, glutamine, and n-3 fatty acids given as supplements enhance or modify immune functions.

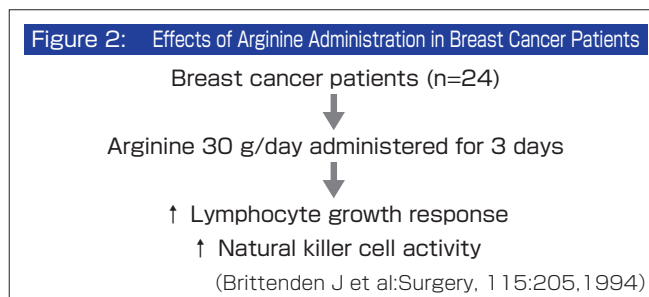
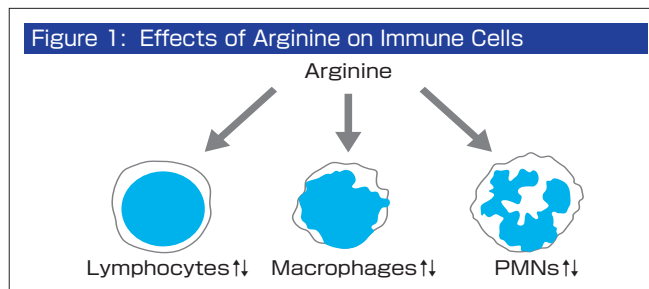
Q.3 Mechanisms for enhanced immune function by arginine include growth hormone or prolactin secretion, polyamine synthesis, and nitric oxide production. Would you please tell us about the specific immune effects of arginine?

A.3 Arginine stimulates secretion of hormones like growth hormone prolactin, insulin and glucagon. Moreover arginine is a nitric oxide precursor that elicits many physiological effects. Arginine is also an essential substance for nucleic acid and polyamine synthesis.

Supplemented arginine affects the functions of immune cells such as lymphocytes, macrophages, and neutrophils. In addition to nitrogen metabolic improvement, arginine promotes wound healing, and suppresses tumor growth (figure 1).

The appropriate administration of arginine enhances

delayed skin hypersensitivity response, lymphocyte growth, lymphocyte IL-2 production, and neutrophil antibacterial capacity. Through these mechanisms arginine may improve the survival rate in experimental bacterial peritonitis. The effects of arginine administration on lymphocyte function in breast cancer patients is shown in figure 2. On the other hand, it is also known that excessive administration of arginine impairs immune function. Therefore it is important to select the appropriate arginine dosage.



● Arginine and Glutamine Play a Vital Role In Immunonutrients

Q.4 What other types of nutrients in combination with arginine would be effective?

A.4 Generally, nutritional components with greater immune enhancing/modulating effects include arginine, ω -3 fatty acids, and glutamine. Components with lesser effects are nucleic acids, vitamins A, C, E, or zinc. These specific nutritional components are sometimes administered separately, but several of them are added or strengthened in immuno-enhancing enteral nutrient preparations. However, there are a theoretically limitless number of combinations of these nutrients when one considers the types and amounts. It is not known at this point what combinations are the most effective.

Q.5 Would you please tell us about the specific effects of such immunonutrients on preventing infection or comorbidities?

A.5 To date there have been several meta-analysis studies that has analyzed clinical trials by immuno-enhancing enteral nutritional preparations. Accordingly, the infection rate in a group receiving

immuno-enhancing enteral nutritional preparations, which included the patients for surgery, patients with injuries, and the critically ill, was 60% of a control group not receiving these preparations. The number of in-hospital days was shorter than the control group by up to 2.5 days. In particular, clinical trials on patients who underwent surgery clearly showed that administration of immuno-enhancing enteral diet immediately after surgery decreased the incidence of infectious complications and reduced the number of days of hospital stay.

Also, very recent meta-analysis study elucidated that such clinical effects were obtained in surgical patients even with a good preoperative nutritional status simply by oral intake once daily for 5 to 7 days before surgery. In surgical patients with a poor preoperative nutritional status, pre- and post-operative administration was effective in preventing post operative complications and in shortening hospital stay. Furthermore, the immuno-enhancing enteral preparations significantly decreased incidences of postoperative intraperitoneal abscess, pneumonia, septicemia, and suture failure (table 1).

Table 1 Effects of immuno-enhancing enteral nutritional preparations: Meta-analysis Cases of gastrointestinal cancer surgery

	Treatment group	Control group	Significant difference
Mortality rate	6/246(2%)	4/251(2%)	None
Infection rate	32/243(13%)	61/244(25%)	Yes
No. of inhospital days	-2.4days		Yes

11 studies 7 IMPACT, 2 Immun-Aid, and 2 others (1,009 patients)
Infections: Pneumonia, intraperitoneal abscess, wound infection, bacteremia (Heys SD, et al: Ann Surg, 229:467, 1999)

Q.6 Would you please say whether there are any direct clinical effects of immunonutrition other than the prevention of infections/comorbidities?

A.6 The medical costs of immuno-enhancing enteral preparations have been investigated in Italy, Germany, and China where the medical systems are different from our own. In all of these countries, medical costs have been cut by the use of immuno-enhancing enteral preparations. Japan also has adopted a lump sum fixed amount payment system at Special-Function Hospitals. For example, when a postoperative infection such as peritonitis, pneumonia or septicemia occurs, these infectious complications increase high medical costs. The longer in-hospital days also decrease reimbursement to the hospital. If the incidence of infection is lowered and the number of in-hospital days is shortened by immuno-enhancing enteral preparations supplemented with arginine, for

example, not only will the patient benefit from lower medical costs, but the hospital will also reduce its total expenditure. Nutritional management using immuno-enhancing enteral preparations will therefore become very significant in terms of hospital management.

● A Growing Awareness of Wide-ranging Functions of Arginine

Q.7 Would you please explain the clinical effects, future applications, and development of L-arginine other than in the field of nutritional immunity?

A.7 As I just mentioned, arginine is a unique amino acid that possesses a multitude of actions. Its effects on different types of conditions are currently under investigation. For example, the diagnosis of growth hormone hyposecretion using its hormone secretory effect, treatment for hypercitrullinemia that is a specific amino acid metabolic disorder, treatment for conditions such as angina pectoris, cardiac failure, coronary artery disease, intermittent claudication, pulmonary hypertension, eclampsia, and impotence due to vasodilator action via NO production, application in the prevention of stent occlusion. The promotion of wound healing in case of bedsores or burns due to an immunoactivation effect, and the treatment of senile dementia and infertility are now under study, as well as the enhancement of chemotherapy effects in tuberculosis, HIV treatment, malignant tumor through antitumor action.

The effects of arginine will become further elucidated after more clinical studies in such conditions. It will also be necessary to study arginine dosage, adverse reactions, and contraindications.

Arginine is thus likely to play an ever-increasing, vital role in improving medical treatment and benefiting patient health. Thank you very much.



Profile of Hideaki Saito, M.D.

Graduated from the Faculty of Medicine, University of Tokyo in 1967. Worked in Surgery, Tokyo Koseinenkin Hospital from 1969 and became chief physician in 1975. Worked in Surgery I, University of Tokyo from 1976, and in 1984 became a researcher in surgery at the University of Cincinnati, USA. He became chief surgeon at Kokuritsu

Ryoyojo, Tokyo Hospital in 1986. He was again affiliated with Surgery I, the University of Tokyo from 1988, and became an assistant professor of Surgery there in 1993. He was promoted to professor in 2002. He became a professor of Department of Healthcare Administration, School of Medicine of Kyorin University