

Arginine Metabolism: Enzymology, Nutrition, and Clinical Significance

Session V: Therapeutic Strategies and Supplementation— Discussion Summary¹

Joseph Loscalzo²

Whitaker Cardiovascular Institute and Evans Department of Medicine, Boston University School of Medicine, Boston, MA 02118

Eric Newsholme pointed out that in invertebrates, the role of creatine phosphate is filled by arginine phosphate, synthesized by arginine phosphokinase. Why vertebrate evolution led to a change in phosphagen from arginine phosphate to creatine phosphate is not clear. To date, arginine phosphate has not been identified in mammals.

Juan Ochoa stated that one of the key conclusions he drew from these presentations is that arginine metabolism is heterogeneous and quite complex. Thus, proposing a straightforward effect of supplemental arginine on a single parameter in this complex catabolism is, at best, naive.

Abdul Traish was asked about the use of arginine and arginase in sexual dysfunction. He stated that arginase inhibitors increased arginine by 2–3-fold and endothelial NO synthase by ~3-fold in vaginal epithelium, and that arginine and arginase inhibitors improved erectile dysfunction in most studies.

When asked whether creatine supplements increase arginine availability as a substrate for NO synthases (by suppressing AGAT synthesis), Robert Wolfe responded negatively, arguing that normal subjects given arginine show no increase in skeletal muscle blood flow or exercise performance. In addition, he thought that the time course of the beneficial effect of creatine on performance was most consistent with its effect on the creatine phosphate pool. Wolfe also stated that he believed the benefits of creatine manifest after repetitive exercise training was likely secondary to a shift in the anaerobic threshold, facilitating the extent to which creatine becomes an important energy source in a better-conditioned individual.

A long discussion then ensued among Juan Ochoa, Paul van Leeuwen, and Bruce Bistrian about the controversial area of arginine supplementation in acutely ill surgical patients. No consensus was reached on the benefit or lack thereof in the broad population of all critically ill patients. Dose-ranging studies are clearly needed in specific populations of patients to whom parenteral nutritional supplements of specific composition are coadministered.

Eric Newsholme asked how nitric oxide is removed and inactivated, pointing out that he knows of no messenger system in the body that relies on spontaneous inactivation. Joseph Loscalzo listed a variety of inactivation mechanisms, including oxidation to nitrite and nitrate; reaction with superoxide and lipid peroxy radicals to form peroxynitrite and lipid peroxynitrites, respectively; formation of S-nitrosothiols of both low-molecular-weight (S-nitrosoglutathione)

and protein-derived (post-translationally modified cysteinyl thiol functionalities) forms; and generation of nitrosyl compounds and of nonheme iron-nitrosyl species. He stated that there is not a specific enzymatic mechanism in eukaryotes responsible for nitric oxide degradation. In plants, nitric oxide can be enzymatically reduced to dinitrogen oxide but no such enzymatic activity is present in vertebrates. Newsholme also asked about the nature of the (protein) binding sites for nitric oxide. Loscalzo stated that it binds to prosthetic heme groups associated with guanylyl cyclase, for example. In addition, there are nitric oxide transporters, the nitrophorins, found in insects that have distinct nitric oxide binding domains.

One last comment was raised regarding the need to begin to study the effects of arginine depletion or supplementation on global gene and protein expression (expression arrays and proteomic analyses) in select cell types. This approach is potentially of great importance in trying to unravel the complex interactions among the many molecular species with which arginine interacts and upon which its metabolism and actions depend.



FOOTNOTES

¹ Prepared for the conference "Symposium on Arginine" held April 5–6, 2004 in Bermuda. The conference was sponsored in part by an educational grant from Ajinomoto USA, Inc. Conference proceedings are published as a supplement to *The Journal of Nutrition*. Guest Editors for the supplement were Sidney M. Morris, Jr., Joseph Loscalzo, Dennis Bier, and Wiley W. Souba. 