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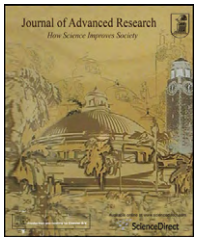

REVIEW

Anti-aging effects of L-arginine

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Abstract L-Arginine is one of the most metabolically versatile amino acids. In addition to its role in the synthesis of nitric oxide, L-arginine serves as a precursor for the synthesis of polyamines, proline, glutamate, creatine, agmatine and urea. Several human and experimental animal studies have indicated that exogenous L-arginine intake has multiple beneficial pharmacological effects when taken in doses larger than normal dietary consumption. Such effects include reduction in the risk of vascular and heart diseases, reduction in erectile dysfunction, improvement in immune response and inhibition of gastric hyperacidity. This review summarises several positive studies and personal experiences of L-arginine. The demonstrated anti-aging benefits of L-arginine show greater potential than any pharmaceutical or nutraceutical agent ever previously discovered.

Metabolism of L-arginine: an entrance to clinical value

L-Arginine is a basic natural amino acid. Its occurrence in mammalian protein was discovered by Hedin in 1895 [1]. L-Arginine is engaged in several metabolic pathways within the human body. It serves as a precursor for the synthesis not only of proteins but also of urea, polyamines, proline, glutamate, creatine and agmatine (Fig. 1) [2]. As part of this, L-arginine is an essential component of the urea cycle, the only pathway in mammals that allows the elimination of toxic ammonia from the body. Ornithine, the by-product of this reaction, is a precursor for the synthesis of polyamines, molecules essential for cell proliferation and differentiation. L-Arginine is also required for the synthesis of creatine, an essential energy source for muscle contraction. Agmatine, which has a clonidine-like action on blood pressure, is also formed from L-arginine, though its physiological function is not yet fully understood. However, current interest in L-arginine is focused mainly on its close relationship with the important signal molecule nitric oxide (NO). L-Arginine is the only substrate in the biosynthesis of NO, which plays critical roles in diverse physiological processes in the human body including neurotransmission, vasorelaxation, cytotoxicity and immunity.

It is worth mentioning that the processes described in Fig. 1 do not all occur within each cell; instead, they are differentially expressed according to cell type, age and developmental stage, diet, and state of health or disease. In fact, Fig. 1 is somewhat misleading in that it summarises the metabolism of arginine at a wholebody level; it does not represent arginine metabolism in any particular cell type, nor does it indicate which enzymes are expressed under different conditions, which enzymes are regulated, the presence of various inter- and intracellular transport systems or how substrates are divided into the different pathways.

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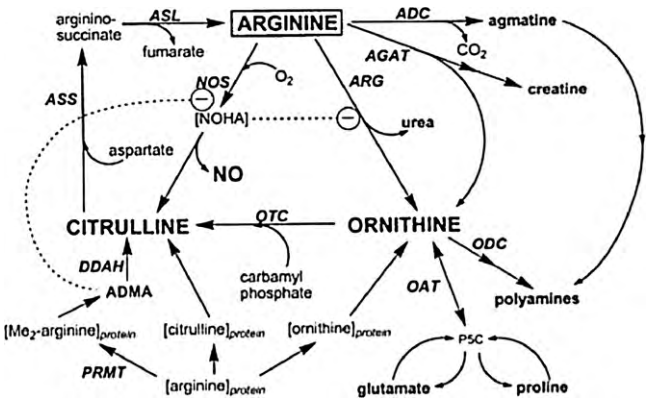

Fig. 1 Overview of mammalian arginine metabolism. Only enzymes that directly use or produce arginine, ornithine, or citrulline are identified, and not all reactants and products are shown. Inhibition of specific enzymes is indicated by dashed lines and the dash within a circle. Amino acid residues within proteins are identified by brackets. Key to abbreviations: ADC, arginine decarboxylase; AGAT, arginine: glycine amidinotransferase; ARG, arginase; ASL, argininosuccinate lyase; ASS, argininosuccinate synthetase; DDAH, dimethylarginine dimethylaminohydrolase; Me2, dimethyl; OAT, ornithine aminotransferase; ODC, ornithine decarboxylase; OTC, ornithine transcarbamylase; P5C, L-D1-pyrroline-5-carboxylate; PRMT, protein–arginine methyltransferase [2].

L-Arginine requirements in humans

L-Arginine is traditionally classified as a semi-essential or conditionally essential amino acid; it is essential in children and non-essential in adults. Homeostasis of plasma L-arginine concentrations is regulated by dietary arginine intake, protein turnover, arginine synthesis, and metabolism. This may explain why, under certain conditions, L-arginine may become an essential dietary component. The main tissue in which endogenous L-arginine synthesis occurs is the kidney, where L-arginine is formed from citrulline, which is released mainly by the small intestine [3]. The liver is also capable of synthesising considerable amounts of L-arginine; however, this is completely reutilised in the urea cycle so that the liver contributes little or not at all to plasma arginine flux [4].

L-Arginine normally constitutes approximately 5–7% of the amino acid content of a typical healthy adult diet. This accounts to an average intake of 2.5–5 g/day, which only meets the body's minimal requirements for tissue repair, protein synthesis and immune cell maintenance. L-Arginine delivered via the gastrointestinal tract (GIT) is absorbed in the jejunum and ileum of the small intestine. A specific amino acid transport system (the y^+ transporter) facilitates this process; this transport system is also responsible for assisting the transport of other basic amino acids L-lysine and L-histidine [5]. About 60% of the absorbed L-arginine is metabolised by the GIT, and only 40% reaches the systemic circulation intact. Most dietary proteins have a relatively balanced mixture of amino acids, and thus the only way to selectively deliver more L-arginine to an individual would be to supplement with the individual amino acid itself.

There is little evidence to support an absolute dietary deficiency as a cause of vascular dysfunction in humans. However, evidence that supports the importance of an exogenous supply of L-arginine for a healthy vascular system has been provided by Kamada et al. [6]. In this study, vascular endothelial function was examined in a lysinuric protein intolerant (LPI) patient that had a genetic defect of dibasic amino acid transport caused by mutations in the SLC7A7 gene. The transporter is normally expressed in intestinal and renal epithelial cells, and deficient expression leads to impaired dietary uptake of exogenous L-arginine and impaired renal tubular reabsorption of filtered L-arginine. As a result, plasma L-arginine concentration in the patient was considerably lower than normal (reduced by 79%).

Assessment of NO-dependent endothelial function in this patient revealed serum levels of nitrogen oxides (NOx) and flow-mediated brachial artery vasodilator response approximately 70% lower than in controls. The patient also suffered from reduced circulating platelet count, increased plasma levels of the thrombin–antithrombin III complex, and elevated plasma fibrin (ogen) degradation products. Intravenous infusion of L-arginine reversed all these effects. The conclusion that can be derived from these results is that the extracellular supply of L-arginine is essential for proper endothelial nitric oxide synthase (eNOS) activity, despite the fact that intracellular L-arginine may far exceed the Km for eNOS, a phenomenon termed in literature 'arginine paradox'. Most investigators believe that this phenomenon is due to the colocalisation of cation arginine transporter (CAT-1) with membrane-bound eNOS in plasmalemmal caveoli [7]. The importance of the external supply of L-arginine suggests the definition of L-arginine as a 'semi-essential' amino acid in adults.

The clinical pharmacology of L-arginine

L-Arginine and the cardiovascular system

Normal plasma arginine concentrations are ~80–120 μM; intracellular concentrations are even greater (up to 1 mM). The Km for arginine as a substrate for the NOS is in the region of 1–10 μM; thus there would appear to be a vast surplus of substrate. Nevertheless, several reports have indicated that administration of exogenous L-arginine may enhance the generation of NO.

In the cardiovascular system, exogenous L-arginine causes a rapid reduction in systolic and diastolic pressures when infused into healthy humans and patients with various forms of hypertension. Furthermore, oral L-arginine supplementation attenuates platelet reactivity and improves endothelial function in animal models of hypercholesterolemia and atherosclerosis. Clinical studies of L-arginine in humans have also been highly positive in improving endothelial dysfunction and even preventing restenosis after balloon angioplasty. An excellent review of the clinical pharmacology of L-arginine, particularly in the cardiovascular system, has been provided by Boger and Bode Boger [8].

A summary of some of the positive results for L-arginine in the prevention and improvement of cardiovascular disease (CVD) include: 6.6 g/day oral in hypercholesterolemic patients with peripheral arterial disease (Heartbar)—at 2 weeks increased pain-free, increased total walking distance (by 66 and 23%), and increased quality of life [9]; 15 g/day oral in patients with congestive heart failure—at 5 days improved glomerular filtration rate, natriuresis and plasma endothelin levels [10]; 2× 3.3 g/day oral in type I diabetic patient with debilitating exertional angina pectoris—at 7 days completely ameliorated angina and normalised exercise capacity [11]; 8.4 g/day oral in hypercholesterolemic humans—at 2 weeks normalised platelet aggregation [12]; 17 g/day oral in healthy non-