

Review Article

DIVERSE POTENTIAL AND PHARMACOLOGICAL STUDIES OF ARGININE

Anju Meshram and Nidhi Srivastava*

Department of Bioscience and Biotechnology, Banasthali University, Banasthali- 304022, Rajasthan, India

Abstract: Arginine is metabolically flexible amino acid with major role in protein synthesis and detoxification of ammonia. It is involved in several metabolic pathways for the production of biologically active compounds such as creatine, nitric oxide, ornithine, glutamate, agmatine, citrulline and polyamines. Regarding this all, we review the crucial role of arginine in metabolism, diversified prospective uses and pharmacological applications. Arginine plays an important role in the treatment of tumorigenesis, asthma, gastric, erectile dysfunction, apoptosis, melanoma and congestive heart failure. Ability to produce nitric oxide offers various applications as in the prevention of age and hair loss. It serves as a precursor of creatine with ergogenic potential. The ability to increase endogenous growth hormone makes arginine a preferred supplement for the improvement of physical performance. In the present study details about the pharmacological applications of arginine based on modern scientific investigations have been discussed. There are immense properties hidden in arginine that need to be explored using the scientific investigations to make it beneficial for the medicine and human health. More research is needed to evaluate the role of arginine supplementation on exercise performance and training adaptations in healthy and diseased populations before taking any conclusions.

Keywords: Arginine; nitric oxide; pharmacology; metabolism

Introduction

L-Arginine is a basic natural amino acid engaged in several metabolic pathways within the human body (Figure 1). Glutamine is an important precursor for de novo synthesis of arginine in humans (Ligthart-Melis *et al.*, 2008). Arg is a substrate for protein synthesis but also modulates cellular biochemical functions via conversion to a number of biologically active compounds such as urea, polyamines, proline, glutamate, creatine and agmatine (Morris, 2006). Arg is utilized by a vast variety of metabolic pathways that produce a variety of biologically active compounds such as nitric oxide, creatine phosphate, ornithine, and citrulline (Tong and Barbul, 2004).

The maintenance of plasma arginine levels is primarily dependent upon its synthesis in the kidney and dietary intake. Dietary arginine is not essential in healthy adult humans, demonstrating the utility of the kidney in this regard. However, it becomes 'essential' in conditions of starvation, injury or stress (Barbul, 1986). Arginine supplementation is therefore beneficial in pathophysiologic settings where systemic arginine levels decrease, such as in models of wound healing, lymphocyte responses and mitogenesis (Satriano 2004). Arginine is finding a wide range of applications in production of proteins. Arginine has been used for many years to assist protein refolding. This effect was ascribed to aggregation suppression by arginine of folding intermediates during protein refolding (Tsumoto *et al.*, 2005).

Arginine has various pharmacological applications such as tumorigenesis, asthma, gastric, erectile dysfunction, apoptosis, melanoma

Corresponding Author: Nidhi Srivastava
E-mail: nidhiscientist@gmail.com

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and congestive heart failure. Remarkable uses of Arg can be seen in the prevention of hair loss, anti-aging, role in cell division, improvement of memory and cognitive functions.

Arginine sources

Arginine can be manufactured by the human body, and does not need to be obtained directly through the diet. The biosynthetic pathway however does not produce sufficient Arg, and some must still be consumed through diet. Legumes, seeds and nuts are usually rich in arginine. The richest source by dry weight is sunflower seeds, followed by carob and butternut squash. Other rich sources are pumpkin seeds, sesame seeds, soybeans, watercress, peanuts, fenugreek, mustard seeds, almonds and Indian figs (Watson and Zibadi, 2012). But the research on Arg refers to supplementation with the free amino acid, which is different from how arginine appears in sunflower seeds and other foods. In food, amino acids are linked together by the hundreds or even thousands and must be broken down to be used by the body. In other words, the arginine present in sunflower seeds, nuts, and legumes within the structure of the proteins, so it cannot be replaced by the synthesized free arginine used for scientific trials (Leigh, 1998).

Arginine methylation

Arginine methylation is a common post translational modification. It occurs on both cytoplasmic and nuclear proteins, and is particularly abundant on shuttling proteins. Arg methylation of the interior histone tails plays various roles in regulating chromatin function. Arginine methyltransferases, a family of protein, is a subset target histones that catalyze methylation reactions (Lorenzo and Bedford, 2011). Protein arginine methyltransferase 6 (PRMT6) is a member of the protein arginine methyltransferase (RMT) family, which comprises 45 enzymes, nine of which are known to catalyze protein arginine N-methylation reactions. These post-translational modifications are important regulators of RNA processing, transcriptional regulation, signal transduction, and other cellular processes (Figure 2) (Mitchell *et al.*, 2015)

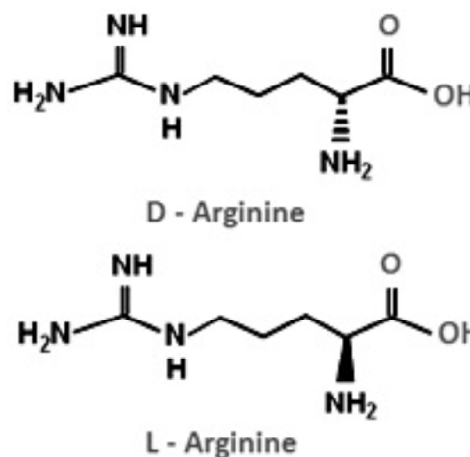


Figure 1: Chemical structure of the two isoforms of arginine: D-Arginine and L-Arginine

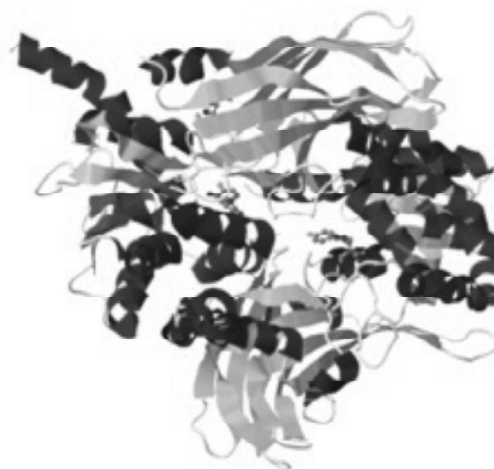


Figure 2: Ribbon representation of the crystal structure of human protein arginine methyltransferase PRMT6 bound to SAH and an aryl pyrazole inhibitor (PDB ID: 4Y2H)

Arginine metabolism

Arginine is metabolized through a complex and highly regulated set of pathways that remain incompletely understood at both the whole body and the cellular levels. The partial reactions of the urea cycle, the L-arginine-NO pathway, a citrulline-NO cycle, and a branch point leading to the formation of guanidino compounds in Arg metabolism occurs in the conifers in eastern Canada (Durzan, 2009). Adding to the metabolic complexity is the fact that limited arginine availability can selectively affect the expression of specific genes, most of which are involved in some aspect of Arg metabolism (Morris, 2006).

Arginine has numerous metabolic fates and thus is one of the most multipurpose amino acids. It is metabolically inter convertible with the

amino acids proline and glutamate, and also serves as a precursor for urea, protein synthesis, nitric oxide, agmatine, creatine and polyamines (Figure 3, 4). These processes do not all occur within each cell but are differentially expressed according to age, cell type, diet, developmental stage and state of health or disease. Currently the picture of Arg metabolism is imperfect and incomplete for any mammalian species. Complete understanding of arginine metabolism will require integration of information obtained from multiple approaches, including genomics, proteomics, and metabolomics (Morris, 2007).

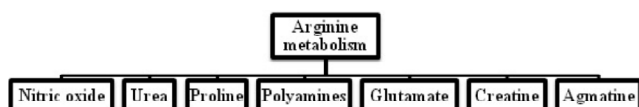


Figure 3: Pictorial representation of arginine as a precursor for various compounds such as urea, protein, nitric oxide, agmatine, creatine and polyamines

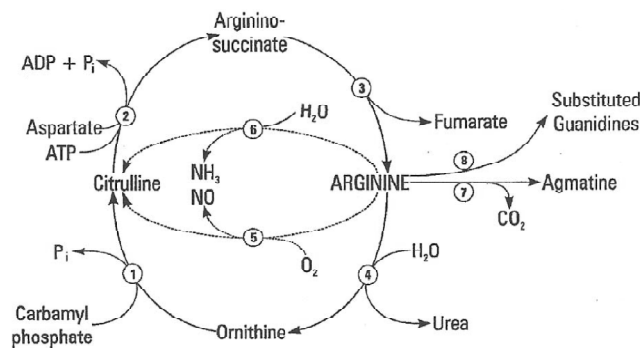


Figure 4: Biosynthetic pathway for the metabolism of arginine

Pharmacological applications

Arginine contributes in various pharmacological applications like tumourigenesis, obesity, asthma, melanoma, gastric environment, erectile dysfunction, programmed cell death and congestive heart failure (Figure 5). Arginine's NO-stimulating effects can be utilized in therapeutic regimens for angina pectoris, congestive heart failure, hypertension, coronary heart disease, preeclampsia, intermittent claudication, and erectile dysfunction. In addition, Arg has been studied in the treatment of HIV/AIDS, athletic performance, burns and trauma, cancer, diabetes and syndrome X, gastrointestinal diseases, male and female infertility, interstitial cystitis, immunomodulation, and senile dementia (Appleton, 2002).

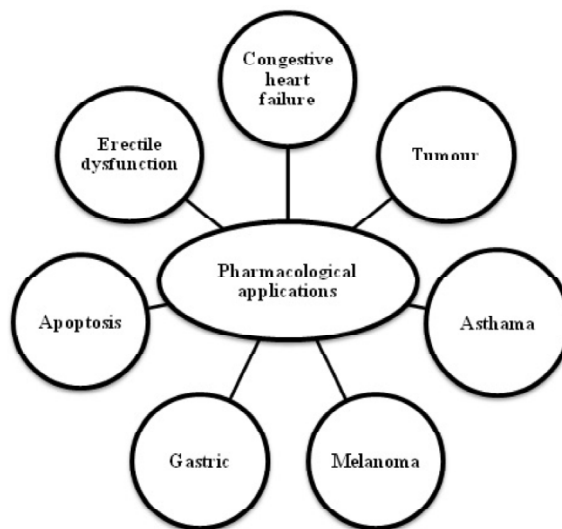


Figure 5: Pictorial representation for the different pharmacological applications of arginine

Arginine methylation contributes to tumourigenesis

In the field of infectious diseases the multifaceted amino acid Arg has reached special attention as substrate for the host production of the antimicrobial agent nitric oxide. A variety of infectious organisms interfere with this part of the host immune response by reducing the availability of Arg (Blackwell and Ceman, 2012).

E2F transcription factors are implicated in diverse cellular functions. The founding member, E2F-1, is endowed with contradictory activities, being able to promote cell-cycle progression and induce apoptosis. However, the mechanisms that underlie the opposing outcomes of E2F-1 activation remain largely unknown. E2F-1 is directly methylated by protein arginine methyltransferase 5 and arginine methylation is responsible for regulating its biochemical and functional properties, which impacts on E2F-1-dependent growth control. Arginine methylation influences E2F-1 protein stability and the enhanced transcription of a variety of downstream target genes reflect increased E2F-1 DNA-binding activity. Importantly, E2F-1 is methylated in tumour cells, and a reduced level of methylation is evident under DNA damage conditions that allow E2F-1 stabilization and give rise to apoptosis. Arg methylation regulates the biological activity of E2F-1 activity, and raise the possibility that arginine methylation contributes

to tumourigenesis by influencing the E2F pathway (Cho *et al.*, 2012).

Nitric oxide- link between obesity and asthma via arginine

Obesity adversely affects asthma severity and control by mechanisms that are not fully understood. Nitric oxide plays a role as a potential mechanistic link between obesity and late onset asthma (>12 years). There is an inverse association between increasing body mass index and reduced exhaled nitric oxide. This is related to nitric oxide synthase uncoupling, which occurs due to an imbalance between L- Arg and its endogenous inhibitor, asymmetric dimethyl arginine (Holguin, 2013).

Arginine and melanoma

Despite recent development of promising immunotherapeutic and targeted drugs, prognosis in patients with advanced melanoma remains poor, and a cure for this disease remains elusive in most patients. The success of melanoma therapy depends on a better understanding of the biology of melanoma and development of drugs that effectively target the relevant genes or proteins essential for tumor cell survival. Melanoma cells frequently lack argininosuccinate synthetase, an essential enzyme for Arg synthesis, and as a result they become dependent on the availability of exogenous Arg. Accordingly, a therapeutic approach involving depletion of available arginine has been shown to be effective in preclinical studies. Early clinical studies have demonstrated sufficient antitumor activity to give rise to cautious optimism (Yoon *et al.*, 2012).

Arginine in programmed cell death

Programmed Cell Death 4 (PDCD4) has been described as a tumor suppressor, with high expression correlating with better outcomes in a number of cancer types. Yet a substantial number of cancer patients with high PDCD4 in tumors have poor survival, signifying that oncogenic pathways may inhibit or change PDCD4 function. PDCD4 has significance in breast cancer and Protein Arginine Methyltransferase 5 (PRMT5) acts as a cofactor that radically alters PDCD4 function. Co-expression of PDCD4 and PRMT5

in an orthotopic model of breast cancer causes accelerated tumor growth and that this growth phenotype is dependent on both the catalytic activity of PRMT5 and a site of methylation within the N-terminal region of PDCD4. These results reveal a new cofactor for PDCD4 that alters its tumor suppressor functions and point to the utility of PDCD4/PRMT5 status as both a prognostic biomarker and a potential target for chemotherapy (Powers *et al.*, 2011).

Arginine in gastric environment

The Arg-dependent extreme acid resistance system helps enteric bacteria survive the harsh gastric environment. At the center of this multi-protein system is an arginine-agmatine antiporter, AdiC. To maintain cytoplasmic pH, AdiC imports arginine and exports its decarboxylated product agmatine, resulting in a net extrusion of one "virtual proton" in each turnover. The random orientation of AdiC in reconstituted liposomes throws up an obstacle to quantifying its transport mechanism (Tsai *et al.*, 2012).

Erectile dysfunction and arginine

There are only very few reports on the improvement of erectile function by L- Arg administration. A study by Chen *et al.* (1999) revealed a significant subjective improvement in sexual function in men with organic erectile dysfunction (31% of cases) after oral intake of 5 g l-arginine for 6 weeks, but only if they had decreased NOx excretion or production. Other studies have shown that long term oral administration of pharmacological doses of L- Arg improves the erectile response in the aging rat (1997) as well as in patients with erectile dysfunction (Melman, 1997; Zorogniotti and Lizza, 1994). However, Klotz *et al.* (1999) reported in a controlled crossover study that oral L- Arg at 3×500 mg/day was not better than a placebo as a first line treatment for the mixed type of impotence.

Arginine in congestive heart failure

L- Arginine may improve cardiac performance in people with congestive heart failure, according to a 2000 study published in Clinical Cardiology. L- Arg exerted a negative chronotropic effect and

improved systemic hemodynamic condition without affecting contractility. Nitric oxide inhalation increased pulmonary capillary wedge pressure and did not change systolic and diastolic cardiac function in severe cardiomyopathy. Our results should encourage further investigations to determine whether endothelial dysfunction in heart failure can be attenuated or partially reversed by L- Arg for a new therapeutic option (Bocchi *et al.*, 2000).

Role of L-Arginine in other physiological response

Arginine as a good source of pharmacological activities also plays a vital role in other biological process (Figure 6).

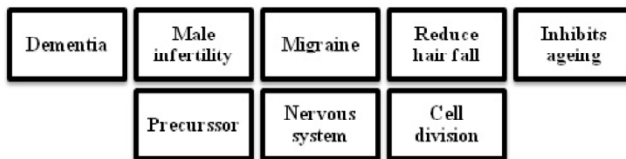


Figure 6: Role of L-Arginine in physiological response

Arginine helps to prevent hair loss

The vasodilatory effect of Arg promotes hair growth as the nitrogen oxide generated from Arg opens the potassium channels of the cells. The blood supply to the hair root is then improves, which in turn stimulates hair growth (Watson and Zibadi, 2013). Arg helps to produce keratin and helps to minimize disease-related hair loss by enhancing immune function. It also protects the hair from the damaging effects of hair colouring and bleaching (Ohimura and Ino, 2004).

Arginine inhibits ageing

Arginine may inhibit one of the primary mechanisms of the aging process cross-linking (Radner *et al.*, 1994). Arg increases the release of the human growth hormone (HGH) (also known as the anti-aging hormone) from the pituitary gland (Gianotti *et al.*, 2000).

Role of arginine in cell division

Arginine plays an important role in cell division, the healing of wounds, removing ammonia from the body, immune function, and the release of hormones (Bishop *et al.*, 2013).

Role of arginine as a precursor to other molecules

Arginine is the immediate precursor of nitric oxide, urea, ornithine and agmatine; is necessary for the synthesis of creatine; and can also be used for the synthesis of polyamines (mainly through ornithine and to a lesser degree through agmatine), citrulline, and glutamate. For being a precursor of nitric oxide, (relaxes blood vessels), Arg is used in many conditions where vasodilation is required (Tapiero *et al.*, 2002).

Arginine in nervous system

Arginine may be useful for the treatment of Alzheimer's disease (due to its ability to repair damaged Axons by increasing polyamines levels) (Tarkowski *et al.*, 2000). Arg has also been reported to present a hydrophobic environment and exist in a supramolecular assemblies and binds to Alzheimer's amyloid beta 1-42 ($A\beta_{1-42}$) which modulates the hydrophobicity of $A\beta_{1-42}$ molecule and suppress fibrillar suppression (Das *et al.*, 2007). Arg (combined with Lysine) may reduce stress induced anxiety (Samriga *et al.*, 2007). Arg may be essential for the regeneration of damaged axons of neurons (its role appears to be as an agent for degrading proteins that have been damaged through axon injury) (Cestaro, 1994). It may facilitate the potency of long term memory (by stimulating the production of nitric oxide, a Neurotransmitter responsible for the potentiation (storage) of long term memory (Pautler, 1994). Arg improves memory and cognitive functions. (Pandhi and Balakrishnan, 1999). Arginine improves pituitary responsiveness and modulates hormonal control (di Luigi *et al.*, 1999).

Cytotoxic role of arginine

Other reported effects of L- Arg include increased quantity and cytotoxic capability of lymphokine-activated and natural killer T-cells in breast cancer (Brittenden *et al.*, 1994). Specifically, patients with cancer have reduced levels of L- Arg due to the increased production of arginase I, causing a decrease in T-cell proliferation and impaired T-cell function. One study found a reduction in stimulated T-cell proliferation when cultured without L- Arg. However, the addition of L- Arg or citrulline allowed for recovery of T-cell proliferation. The investigators concluded that

tumor cell regulation of amino acid availability is possibly what allows these cells to escape the immune response (Rodriguez *et al.*, 2007).

Ergogenic response

Ergogenic response of arginine has also been reported by Chromiak and Antonio (2002). The role of arginine supplementation on healthy and diseased populations has to be concluded (Campbell, 2004).

Side effects of L-arginine

Oral administration of L-Arg (up to 30 g/day) in humans does not appear to cause any major adverse reactions, with only infrequent reports of nausea and diarrhea (Shah and Shah 2004; Battaglia *et al.*, 2002). In a trial of malnourished patients with head and neck cancer, the incidence of diarrhea was higher compared with standard therapy (de Luis, 2004). No adverse reactions were reported with L-Arg 9 g/day over 6 months (Ceremuzyński *et al.*, 1997). Higher doses may be associated with a bitter taste and may affect patient compliance (Chagan *et al.*, 2002).

Conclusion

Various symptoms can be reduced with the help of arginine, which is a semi-essential amino acid for good reason and has a decisive impact on numerous vital processes. Pharmacological use of arginine in demand today to reduce various symptoms and it is no longer possible to imagine orthomolecular medicine without this vital substance.

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Abbreviations

Arginine: Arg, NO: Nitric Oxide, PDCD4: Programmed Cell Death 4, PRMT5: Protein Arginine Methyltransferase 5, LDL: Low Density Lipoprotein

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