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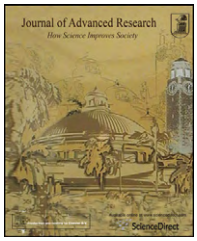

REVIEW

Anti-aging effects of L-arginine

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KEYWORDS

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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.

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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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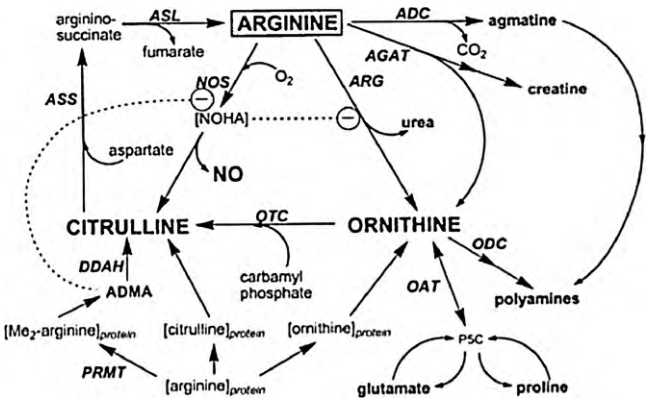

Fig. 1 Overview of mammalian arginine metabolism. Only enzymes that directly use or produce arginine, ornithine, or citrulline are identified, and not all reactants and products are shown. Inhibition of specific enzymes is indicated by dashed lines and the dash within a circle. Amino acid residues within 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-

Table 1 Clinical conditions with elevated ADMA [16].

Condition	Fold increase vs. controls
Hypercholesterolemia	2–3
Hypertriglyceridemia	2
Hypertension	2
Pulmonary hypertension	2–3
Peripheral arterial disease	2–4
Chronic renal failure	2–12
Congestive heart failure	2–3
Type 2 diabetes	2
Preeclampsia	2

smoking elderly population—at 14 days decreased serum total cholesterol (TC) and decreased low density lipoproteins cholesterol (LDL-C), but not decreased high density lipoproteins cholesterol (HDL-C) [13]; long-term oral L-arginine reduced restenosis after experimental angioplasty [14]; reduced intimal thickening in vein grafts [15].

Most reports ascribe the clinical benefits of L-arginine in CVD to the provision of NO. L-Arginine is the only precursor for NOS reaction. NO is produced by all tissues of the body and plays particularly important roles in cardiovascular homoeostasis. Several studies have shown that L-arginine improves vascular function by overcoming the deleterious effects of asymmetric dimethylarginine (ADMA), a novel cardiovascular risk factor. ADMA is a competitive inhibitor of NOS and has been found to be elevated in serum in many diseases (Table 1) [16].

In a recent study from our lab [17], we provided evidence that ADMA (along with other CVD risk factors malondialdehyde (MDA), homocysteine and myeloperoxidase (MPO) activity) was elevated in sera of 15 renal failure patients on hemodialysis. Oral L-arginine administration (15 g/day, 5 g t.i.d. for 1 month) in these patients caused significant reduction in these biochemical markers (Fig. 2).

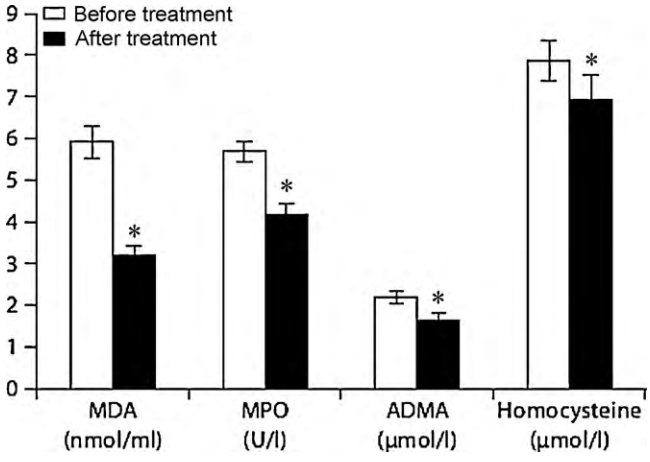

Fig. 2 Effect of oral L-arginine administration (15 g/day, 5 g t.i.d. for 1 month) on MDA, MPO, ADMA and homocysteine levels in 15 renal failure patients on hemodialysis and suffering from CVD. CVD events were defined as: acute myocardial infarction diagnosed by typical clinical and ECG changes, angina pectoris based on typical clinical characteristics or transitory ischemic events verified by echocardiography. Data are represented as mean ± SD. Differences between groups were compared using a one-way analysis of variance (ANOVA) followed by LSD post hoc analysis. *Statistically significant from before oral L-arginine administration at $p \leq 0.05$ [17].

Table 2 NO-dependent and -independent cardiovascular actions of L-arginine.

NO-dependent vascular actions
↑ Vasodilator tone [18]
↓ Leukocyte adhesion [19]
↓ Platelet aggregation [20]
↓ SMC proliferation [21]
↓ Superoxide production [22]
↓ Endothelial dysfunction [23]

NO-independent vascular actions
↓ Angiotensen-converting enzyme activity [24]
↓ Thromboxane B2 formation, fibrin & platelet-fibrin complex [25]
↓ Blood viscosity [26]
↓ Leukocyte adhesion to non-endothelial matrix [27]
↓ LDL oxidation [28]

Non-specific cardiovascular effects
Increases the synthesis of urea, creatine, proline, polyamines and release of hormones as insulin, growth hormone, glucagon and prolactin [8]

Thus, within the scope of NO-dependent and NO-independent vascular actions of L-arginine (Table 2) accumulating evidence supports the clinical use of L-arginine as an anti-atherosclerotic supplement.

L-*Arginine and sexual function*

Arginine is required for normal spermatogenesis. Over 50 years ago, researchers found that feeding an arginine-deficient diet to adult men for 9 days decreased sperm counts by ~90% and increased the percentage of non-motile sperm approximately 10-fold [29]. Oral administration of 500 mg arginine–HCl per day to infertile men for 6–8 weeks markedly increased sperm counts and motility in a majority of patients, and resulted in successful pregnancies [30].

There are only very few reports on the improvement of erectile function by L-arginine administration. A study by Chen et al. [31] 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-arginine improves the erectile response in the aging rat [32] as well as in patients with erectile dysfunction [33,34]. However, Klotz et al. [35] reported in a controlled crossover study that oral L-arginine at 3× 500 mg/day was not better than a placebo as a first line treatment for the mixed type of impotence.

In general, studies in this area are scarce and provide inconsistent results. Further studies, particularly of long-term usage of L-arginine, are needed to distinguish the group of patients that can most benefit from this supplement. The theoretical basis of these studies is furnished by the established crucial role of NO from nerves and possibly endothelia in initiating and maintaining intracavernous pressure increase, penile vasodilatation, and penile erection that are dependent on cyclic GMP synthesised with activation of soluble guanylyl cyclase by NO in smooth muscle cells [36]. The aphrodisiac properties of L-arginine have not been adequately studied, despite the noticeable presence of L-arginine in most aphrodisiac and sexual stimulation formulas commercially available in the international market.

L-*Arginine and the gastrointestinal tract*

NO donors have been repeatedly shown to protect gastric mucosa against damage induced by various agents [37,38]. In addition, reports from different laboratories have demonstrated the importance of endogenous NO in the protection of gastric mucosa. Two studies from Pique's laboratory [39,40] have shown that NO plays a vasodilatory role in gastric microcirculation during acid secretion. Other studies have accredited the role of NO as an endogenous modulator of leukocyte adhesion [41]. In support, Calatayud et al. [38] have shown that transdermal nitroglycerine protected against indomethacin-induced gastric ulceration through maintenance of mucosal blood flow and reduction of leukocyte–endothelial cell rolling and adherence. Moreover, Wallace [42] has stated that reduction of gastric blood flow is the main predisposing factor in the induction of non-steroidal anti-inflammatory drugs (NSAID) gastropathy. Other than the role of NO in maintenance of blood flow, NO may protect against NSAID damage by promotion of prostaglandin synthesis. A mutual interaction has been observed between NOS and cyclooxygenase (COX) enzymes. NO donors were shown to enhance COX activity whereas NOS inhibitors blocked prostaglandin E2 (PGE2) production [43].

In a study from our lab [44], we demonstrated the role of NO in protecting against indomethacin-induced gastric ulceration. Intraperitoneal (i.p.) injection of L-arginine (300 mg/kg) 30 min before i.p. injection of 30 mg/kg indomethacin to rats almost completely protected the rats against indomethacin-induced gastric ulceration by a mechanism independent of modulation of acid secretion, mucin content or pepsin activity, but via maintenance of mucosal NO. On the other hand, pretreatment of rats with the NOS inhibitors L-NAME (50 mg/kg), a non-selective constitutive nitric oxide synthase/inducible nitric oxide synthase (cNOS/iNOS) inhibitor, or the selective iNOS inhibitor aminoguanidine (AMG) (50 mg/kg) worsens the ulcer index (the sum of the length (mm) of all lesions in the fundic region) (Fig. 3). In support to the anti-ulcerogenic effect of L-arginine, reports by Lazaratos et al. [45] and Jimenez et al. [46] have indicated the protective role of L-arginine against the ulcerogenic action of endothelin-1 and ibuprofen, respectively.

Reports have not restricted the role of NO to gastric protection, but also discussed the acceleration of ulcer healing. Konturek et al. [47] have shown that glyceryl trinitrate is capable of ulcer healing and that suppression of NO synthesis resulted in impaired ulcer healing. It is possible that NO directly accelerates ulcer repair by promoting the growth of smooth muscles, as suggested by Hogaboam et al. [48].

In a recent study (in press), we have tested the effect of NO modulation on peptic ulcer healing using the NO precursor; L-arginine, a competitive inhibitor of NOS, L-NAME and the NO donor; nitroglycerine (NTG). Rats were injected with a single oral dose of indomethacin (30 mg/kg) and then treated with L-arginine, NTG or L-NAME, once daily for 7 days starting 4 h after the indomethacin injection. Gross lesion examination and histological assessment were done. Gastric tissue content of NO, PGE2 and mucin were detected. In addition, oxidative stress markers including glutathione (GSH) and lipid peroxides were measured. L-Arginine and NTG were found to accelerate the healing of indomethacin-induced ulcers, as evident in macroscopic and histological examination, to restore normal levels of NO and GSH and to significantly attenuate the increase in PGE2 and lipid peroxides induced by indomethacin. On the other hand, L-NAME was found to exacerbate the mucosal damage (Table 3).

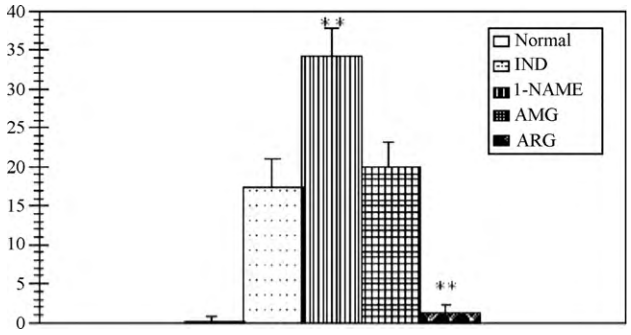

Fig. 3 Ulcer index (mm) of normal, indomethacin, L-NAME, aminoguanidine, and L-arginine treated rats. Results are mean ± SEM of 6–10 animals. **Significantly different from indomethacin at $p < 0{:}01$.

In parallel, Brzozowski et al. [50] have shown that intragastric administration of L-arginine (32.5–300 mg/kg/day) enhanced the healing rate of acetic acid-induced ulcers in a dose-dependent manner, while D-arginine was not effective.

L-*Arginine and wound healing*

Wound healing involves platelets, inflammatory cells, fibroblasts and epithelial cells. All of these cell types are capable of producing NO either constitutively or in response to inflammatory cytokines. NO produced by both iNOS and eNOS plays many important roles in wound healing, from the inflammatory phase through to scar remodeling. NO has cytostatic, chemotactic and vasodilatory effects during early wound repair, regulates proliferation and differentiation of several cell types, modulates collagen deposition and angiogenesis, and affects wound contraction (Fig. 4) [51].

L-Arginine was first noted to enhance wound healing in 1978 [52]. Since then dietary L-arginine has been shown to improve colla-

Table 3 Gross examination of the effect of treatment with L-arginine, NTG or L-NAME on gastric ulcer induced by indomethacin in rats.

Groups	No. of dead rats	Ulcer No.	Ulcer index (mm)	Ulcer score
Control	0	0	–	–
Indomethacin	3	13.25 ± 0.75	19.0 ± 1.45	3.62 ± 0.26
Indomethacin + L-arginine	1	0	–	–
Indomethacin + NTG	2	0	–	–
Indomethacin + L-NAME	5	17.11 ± 0.65	23.2 ± 1.15	4.55 ± 0.17

Gastric ulcer was induced by a single oral injection of indomethacin (30 mg/kg), and then 4 h later, treatment schedule was given daily for 1 week as follows: L-arginine (200 mg/kg), NTG (1 mg/kg) and L-NAME (15 mg/kg). Measurements were done 7 days later. Values given are means of 10–15 observations ± SEM. Ulcer index = sum of lengths of all lesions in each stomach; ulcer score indicates severity of gastric lesion, where **1** (ulcerated area 1–6 mm^2), **2** (ulcerated area 7–12 mm^2), **3** (ulcerated area 13–18 mm^2), **4** (ulcerated area 19–24 mm^2) and **5** (ulcerated area > 24 mm^2) [49].

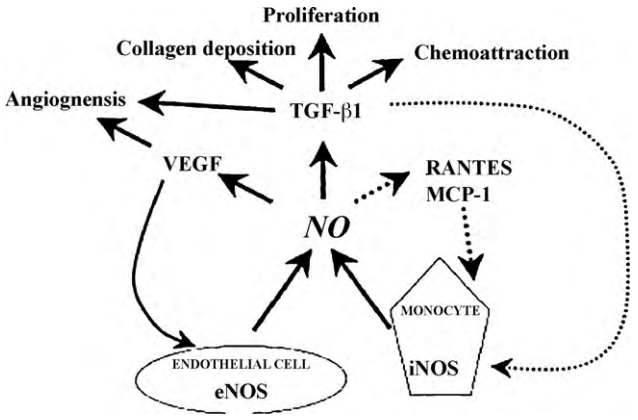

Fig. 4 Schematic of the hypothesised roles of NO in wound healing. Production of NO from eNOS or iNOS leads to modulation of cytokines (e.g., MCP-1, RANTES, VEGF, and TGFb1), which in turn modulates the various facets of wound healing (e.g., chemoattraction, proliferation, collagen deposition, and angiogenesis) [51].

gen deposition and wound strength in both humans [53] and animals [54]. This effect may be due in part to the subsequent increase in production of ornithine by the action of arginase enzyme, a precursor of L-proline during collagen synthesis [55]. The direct role of NO as a cofactor in the promotion of wound healing by L-arginine has also been reported [56]. L-Arginine might improve wound immune cell function by decreasing the inflammatory response at the wound site [57].

The healing effect of L-arginine is also extended to cover burn injuries. Oral dietary L-arginine supplementation of 100–400 mg/kg/day shortened re-epithelisation times, increased amounts of hydroxyproline, and accelerated the synthesis of reparative collagen in burned rats [58]. Burn injuries significantly increase arginine oxidation and fluctuations in arginine reserves. Total parenteral nutrition (TPN) increases conversion of arginine to ornithine and proportionally increases irreversible arginine oxidation. These make arginine conditionally essential in severely burned patients receiving TPN [59].

L-*Arginine and insulin sensitivity*

Diabetes is associated with reduced plasma levels of arginine [60] and elevated levels of the NOS inhibitor ADMA [61]. Evidence suggests that arginine supplementation may be an effective way to improve endothelial function in individuals with diabetes mellitus (DM) [62]. As well, low dose IV arginine has been shown to improve insulin sensitivity in obese, type 2 DM, and healthy subjects [63]. Arginine may also counteract lipid peroxidation and thereby reduce microangiopathic long-term complications of DM [64].

A double-blind trial found oral arginine supplementation (3 g three time/day, 1 month) significantly improved, but did not completely normalise, peripheral and hepatic insulin sensitivity in patients with type 2 DM [65]. Moreover, L-arginine regulates insulin release by NO-dependent [66] and NO-independent [67] pathways.

L-*Arginine and CNS function*

Very few articles have investigated the effects of L-arginine supplementation on CNS function. However, accumulating evidence is beginning to indicate that NO plays a part in the formation of memory [68]. *In vitro*, after specific receptor stimulation, NO is released from a postsynaptic source to act presynaptically on one or more neurons. This leads to a further increase in the release of glutamate and, as a result, to a stable increase in synaptic transmission, a phenomenon known as long-term potentiation. This is thought to be linked to memory function (Fig. 5) [69]. Experiments in animals also suggest that NO is involved in memory, because inhibiting NO synthesis *in vivo* impairs learning behaviour [70].

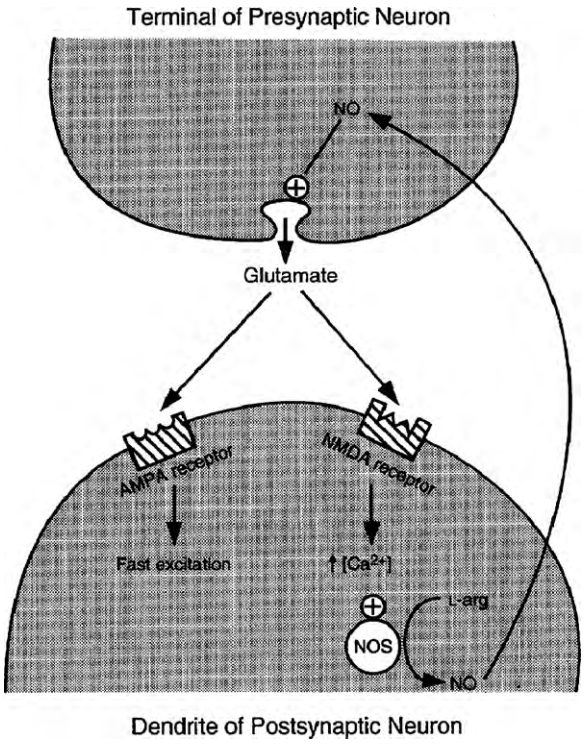

Fig. 5 The role of nitric oxide in the long-term potentiation of neuronal activity. Glutamate released from the presynaptic nerve terminal activates different types of receptors on the dendrites of the postsynaptic neuron. Under normal conditions the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors mediate most of the effects of glutamate. During high-frequency synaptic transmission, however, the activation of N-methyl-D-aspartate (NMDA) receptors results in an increase in intracellular calcium, which stimulates the constitutive nitric oxide synthase (NOS). The nitric oxide (NO) that is produced diffuses back to the presynaptic neuron, where it enhances the release of glutamate. The increased glutamate release leads to greater activation of postsynaptic glutamate receptors, thereby increasing the effectiveness of that synapse. Plus signs indicate stimulation, and L-arg denotes L-arginine [69].

L-Arginine (1.6 g/day) in 16 elderly patients with senile dementia has been found to be effective in reducing lipid peroxidation and increasing cognitive function [71]. In their recent report, Jing et al. [72] explored the possible role of L-arginine in Alzheimer's disease (AD), taking into consideration known functions for L-arginine in atherosclerosis, redox stress and the inflammatory process, regulation of synaptic plasticity and neurogenesis, and modulation of glucose metabolism and insulin activity. They provided evidence that L-arginine may play a prominent role in protection from age-related degenerative diseases such as AD. Further investigation is still needed to cover this virgin area of research.

L-Arginine and muscular activity

L-Arginine has been purported to have ergogenic potential [73]. Athletes have taken arginine for three main reasons: (1) its role in the secretion of endogenous growth hormone; (2) its involvement in the synthesis of creatine; (3) its role in augmenting nitric oxide. In a double-blind study, the effect of a 4-week treatment with arginine aspartate on 21 athletes was assessed [74]. The treated group showed enhanced maximal oxygen consumption as well as a significantly decreased plasma lactate concentration at work intensity of 200, 300 and 400 W (running workout) on the treadmill as compared to the control group. In another study, 8 weeks of oral L-arginine administration (3 g) to 20 male subjects on an exercise program with weights caused a significant increase in muscle strength and mass as compared to the non-treated group [75].

Duchenne muscular dystrophy (DMD) is a lethal, X-linked disorder associated with dystrophin deficiency that results in chronic inflammation, sarcolemma damage, and severe skeletal muscle degeneration. Recently, the use of L-arginine, the substrate of neuronal nitric oxide synthase (nNOS), has been proposed as a pharmacological treatment to attenuate the dystrophic pattern of DMD. Hnia et al. [76] were able to demonstrate that L-arginine decreases inflammation and enhances muscle regeneration in mdx mice (an animal model of Duchenne myopathy). The inhibitory effect of L-arginine on the NF-kappaB/Metalloproteinase cascade reduces beta-dystroglycan cleavage and translocates utrophin and nNOS throughout the sarcolemma. Evidence suggests that L-arginine upregulates utrophin in muscles, which could compensate for the lack of dystrophin in DMD. Utrophin has over 80% homology with dystrophin [77].

Other effects of L-arginine

Other than the benefits in the above stated conditions, L-arginine has been demonstrated to improve peripheral circulation [78], renal function [79], and immune function [80]. It also possesses antistress and adaptogenic capabilities [81]. L-Arginine stimulates the release of growth hormone [82] as well as the release of pancreatic insulin and glucagon and pituitary prolactin [8]. The antioxidant property of L-arginine has been well documented in several reports [83,64]. An interesting article by Grasemann et al. [84] has demonstrated an acute and transient improvement of pulmonary function in cystic fibrosis patients by a single inhalation of L-arginine. Nebulised L-arginine significantly increased exhaled nitric oxide concentrations.

Therapeutic use of L-arginine supplement

L-Arginine is available commercially in several countries in variable dosage forms and mostly indicated as a nutritional supplement. It is available as capsules, tablets, powder, effervescent granules, injection, infusion, and cream with a very wide range of doses. The indications also are quite inconsistent. Amongst the many indications provided on the commercial forms of L-arginine are: prevention and improvement of ischemic heart disease, improvement of microcirculation, improvement of erectile function, improvement of physical exercise capacity, reduction of high blood pressure, improvement of local tissue blood supply and oxygenation, improvement of creatine transport, increase of energy levels, antioxidant, stimulation of dopamine, adrenaline and noradrenaline release, increase of growth hormone production, improvement of wound healing, enhancing immunity, help to reverse atherosclerosis, management of metabolic alkalosis, aphrodisiac, enhancement of sperm mobility and viability, and treatment of interstitial cystitis. L-arginine is also available commercially as a vaginal lubricant and sexual enhancer cream.

Currently, two large multinational pharmaceutical companies are interested in marketing products of L-arginine; the first company produces a product formed of L-arginine with vitamins C and E and marketed as an aid in the recovery of wounds, burns and surgery. The second company is currently recruiting participants for the phase IV clinical trial of oral L-arginine aspartate in the muscular fatigue of the quadriceps, expressed in terms of the fatigue resistance factor (FRF).

Safety considerations

Of the available studies on orally administered L-arginine in humans, few reported any adverse effects following acute or chronic treatment. Doses up to 30 g/day have been generally well tolerated, with the most common adverse effects of nausea and diarrhoea being reported infrequently at higher doses—from 15 to 30 g [85]. No changes in liver function, blood glucose, or plasma electrolytes have been reported. In the absence of appropriately designed safety studies, caution should be taken if L-arginine is used in infants, pregnant

Table 4 Most noticeable observations of the subjects at the end of the 4-week study.

Feature	% of cases (total = 21 cases)		
	Remarkable improvement	Mild improvement	No change
Mental capability			
Ability to concentrate	55	35	10
Memory retrieval	55	35	10
Delay in mental exhaustion	75	15	10
Reduction in severity of anxiety and stress	60	20	20
Reduction in nervousness	72	21	7
Deepness of sleep	80	10	10
General mood	70	25	5
Muscular activity			
Muscular performance	75	5	20
Delay in muscular exhaustion	60	15	25
Sexual performance in males	54	33	13
Overall feeling of well being	65	20	15

Table 5 Additional observations at the end of the 4-week study reported by some subjects.

1. Adjustment of blood pressure in mild hypertension.
2. High energy, especially in the morning when waking up.
3. Clear mind.
4. Stamina and resistance to depression and anxiety.
5. Increase in urine output.
6. Improvement of hair and nail growth and hardness.
7. Improvement of skin texture and appearance.
8. Increase in night dreams.
9. Improvement of circulation and temperature of extremities.
10. Reduction of hyperacidity.
11. Overall improvement of GIT system and defecation.
12. Improvement of most vital activities greatly affected in diabetics, including: reduction of neuritis, improvement of glucose metabolism, enhancement of libido and sexual performance and adjustment of body weight.

or lactating individuals, and those with viral infections and serious compromised renal or hepatic function.

L-Arginine: anti-aging pilot study

In an open-label randomised limited study conducted by the author, 5 g/day L-arginine base was administered orally once at night for 28 days in 21 subjects with age ranging between 41 and 75 years old (14 between 41 and 49 years, 4 between 50 and 59 years, 2 between 60 and 69 years, and 1 between 70 and 79 years), 16 were males and 5 females, 17 were non-smokers and 4 smokers, and 18 of the 21 subjects were taking other medications to control either hypertension, myocardial ischemia, diabetes, gastro-oesophageal reflux disease (GERD) and hyperacidity, hypothyroidism, neuritis, or rheumatoid. All recruited subjects gave written informed consent that complied with the principles of the Helsinki declaration.

A questionnaire was given to the subjects to be completed weekly for 4 weeks. The subjects were advised to write their health status before and after taking L-arginine. The questionnaire included 30 points regarding their mental, muscular, sexual, circulatory, GIT, and other functions during the 4-week administration. Scoring was recorded from 1 to 5; 1 was a remarkable improvement, 2 was a mild improvement, 3 no difference, 4 was worse than before, and 5 was not applicable. The subjects were also advised to report any adverse reactions developed during the administration of the supplement. In addition, they were asked if they wanted to continue taking the supplement after termination of the study. Tables 4 and 5 summarise the most noteworthy information of this pilot study.

At the end of the study, none of the 21 cases experienced any side effects or aggravation of health problems from L-arginine administration. All the 21 cases wanted to continue taking the supplement after termination of the study.

Conclusions

Many – if not all – of the body functions described in this text are debilitated by aging. Studies have shown that L-arginine, through its versatile metabolic and physiological pathways, can improve many of these functions. To summarise some of its effects; L-arginine is involved in the production of a variety of enzymes, hormones, and structural proteins. It facilitates the release of growth hormone, insulin, glucagon, and prolactin. It is a component of the hormone vasopressin, produced by the pituitary gland. It is the physiological precursor of diverse biological compounds such as nitric oxide, polyamines, proline, glutamate, creatine, agmatine and urea. As a booster of immunity, arginine stimulates the thymus and promotes lymphocyte production. This may be an important key for arginine's ability to promote healing of burns and other wounds. Arginine has a positive effect on cerebral as well as systemic circulation. It enhances sexual performance in males. It protects from – as well as heals – gastric ulcers induced by various agents. The demonstrated anti-aging benefits of L-arginine show promises greater than any pharmaceutical or nutraceutical agent ever previously discovered.

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