CARDIOLOGY

THE ROLE OF L-ARGININE IN THE PATHOGENESIS OF ESSENTIAL ARTERIAL HYPERTENSION

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ABSTRACT

The role of arginine in the development of primary arterial hypertension continues to be clarified up to the present moment. During natural metabolic processes in cells, methylated forms of arginine are produced – symmetric (SDMA) and asymmetric (ADMA) dimethylarginine. ADMA is a nitric oxide synthase inhibitor and is now considered a well-established marker for endothelial dysfunction. SDMA is not a nitric oxide synthase inhibitor, but may indirectly reduce nitric oxide production through competitive interaction with cellular L-arginine.
Currently, arginine preparations are practically not used for the treatment of primary arterial hypertension. This was the rationale for the given scientific review. The article summarizes the information available in the literature (2018–2022) on the pathogenetic mechanisms of the relationship between arginine and the development of impaired vascular tone. We used PubMed and RSCI databases for our review. Using keywords, 1784 publications were found over the past 5 years. The final selection criteria were time frame and matching keywords. The review provides data on the increased ADMA concentrations in experimental hypertensive animals and individuals with essential hypertension. The role of arginine metabolites in the genesis of endothelial dysfunction and arterial hypertension and the prospects for the therapeutic use of this compound are discussed.

Key words: *primary arterial hypertension, arginine, symmetrical dimethylarginine, asymmetrical dimethylarginine, citrulline, nitric oxide, nitric oxide synthase, comorbidity*

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L-АРГИНИН И АРТЕРИАЛЬНАЯ ГИПЕРТЕНЗИЯ: КЛИНИКО-ПАТОГЕНЕТИЧЕСКИЕ ВЗАИМОСВЯЗИ И КОМОРБИДНОСТЬ

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РЕЗЮМЕ

Роль аргинина в развитии первичной артериальной гипертензии до настоящего времени продолжает уточняться. Во время естественных обменных процессов в клетках образуются метилированные формы аргинина – симметричный (SDMA, symmetric dimethylarginine) и асимметричный (ADMA, asymmetric dimethylarginine) диметиларгинин. ADMA является ингибитором синтазы окиси азота и в настоящее время рассматривается в качестве общепризнанного маркера эндотелиальной дисфункции. SDMA не является ингибитором синтазы окиси азота, однако может косвенно снижать продукцию окиси азота посредством конкурентного взаимодействия с клеточным L-аргинином.

В настоящее время препараты аргинина практически не используются для лечения первичной артериальной гипертензии. Это явилось обоснованием данного научного обзора. Статья обобщает имеющуюся в литературе информацию (2018–2022 гг.), посвящённую патогенетическим механизмам взаимосвязи аргинина с развитием нарушения сосудистого тонуса. Использованы базы данных PubMed, РИНЦ. По ключевым словам найдены 1784 публикации за последние 5 лет. Критериями окончательного отбора были временные рамки и совпадение ключевых слов. В обзоре приведены данные о повышении концентрации ADMA у экспериментальных гипертензивных животных и лиц с эссенциальной гипертензией; обсуждена роль метаболитов аргинина в генезе эндотелиальной дисфункции и артериальной гипертензии и перспективы терапевтического использования данного соединения.

Ключевые слова: *первичная артериальная гипертензия, аргинин, симметричный диметиларгинин, асимметричный диметиларгинин, цитруллин, оксид азота, синтаза оксида азота, коморбидность*

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Essential hypertension is the most common non-communicable disease, occurring in more than 30–45 % of the population worldwide and in the Russian Federation. The prevalence of this pathology determines the risk of coronary heart disease, myocardial infarctions, strokes, dementia, chronic kidney disease [1]. This determines the constant attention of scientists and clinicians to the pathogenesis of high blood pressure (BP). In our country, the term «hypertensive heart disease», proposed in 1948, is traditionally used. G.F. Lang, to define a disease whose main symptom is an increase in BP that is not associated with pathology leading to secondary hypertension. Overseas, the terms «essential hypertension» and/or «arterial hypertension» (AH) are synonymous with this diagnosis.

The founders of the pathogenetic links in the formation and progression of hypertension are G.F. Lang and A.L. Myasnikov, who described the neurogenic theory of hypertension. These days it is a recognised section of pathogenesis related to activation of the sympathoadrenal system. Since this mechanism of BP increase is realised mainly through alpha- and beta-adrenoreceptors, beta-adrenoreceptor blockers are widely used in the clinic [2]. Alpha-blockers are used less frequently, mainly in therapy-resistant hypertension and in individuals with benign prostatic hyperplasia.

Essential hypertension has been studied from various perspectives, ranging from genetics [3, 4], physiology [5], and in recent years microbiota [6-8] as previously underestimated areas of knowledge contributing to the identification of the aetiology of the disease. Dysfunction of the endothelium with predominant production of vasoconstrictor substances with a simultaneous decrease in the production of bradykinin, nitric oxide, prostacyclin and other compounds that reduce vascular tone plays a crucial role in the formation of hypertension.

Each direction individually has made unique contributions to the understanding of the different mechanisms of BP regulation. However, metabolic dysfunction as one of the links in the pathogenesis of primary arterial hypertension (PAH) is poorly understood. The amino acid L-arginine serves as the main substrate for nitric oxide (NO) production in blood vessels. NO has been called the «molecule of the twentieth century», as the use of drugs based on this molecule significantly improved the prognosis of patients not only with cardiovascular diseases, but also with other pathologies. L-arginine has previously been evidenced to reduce systemic blood pressure in some forms of experimental hypertension, but the comorbid pathology is poorly understood. Previous studies, although not uniform, have revealed positive results of the effects of L-arginine supplementation on endothelial function. As yet, however, they have not found widespread use in clinical practice. The above was the rationale for this scientific review.

THE AIM

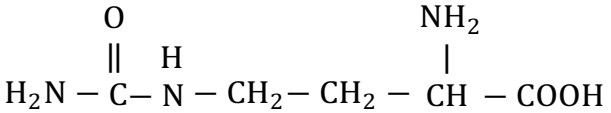
Study of the arginine role in the regulation of endothelial function and vascular tone.

This review summarises the information available in the literature (2018–2022) addressing the pathogenetic mechanisms of arginine's relationship with the development of vascular tone disorders. We used PubMed and RSCI databases for our review. The key words for the search were «primary arterial hypertension», «arginine», 'symmetrical dimethylarginine', 'asymmetrical dimethylarginine', 'citrulline', 'nitric oxide', and 'nitric oxide synthase'. 1,784 publications were found by keywords, mostly in the last 5 years. The final selection criteria were time frame and matching keywords.

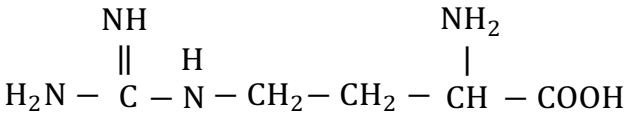
1. ROLE OF ARGININE IN PHYSIOLOGICAL CONDITIONS

In 1998, American scientists Louis J. Ignarro, Ferid Murad and Robert Francis Furchgott were awarded the Nobel Prize in Physiology and Medicine for their discovery of the role of nitric oxide as a signalling molecule in the regulation of the cardiovascular system. With the discovery of the NO role, new opportunities for the treatment of cardiovascular diseases have emerged.

L-arginine, hereinafter referred to as arginine, is a semisubstitutable or conditionally essential amino acid since it can be synthesised by healthy individuals [9]. The name comes from the Greek word ἄργυρος (silver), the typical colour of arginine nitrate crystals. Its chemical formula is 2-amino-5-guanidinopentanoic acid. In the body, arginine is synthesized from L-citruline. The L-citruline molecule is converted by argininosuccinate synthase enzymes into an intermediate product, argininosuccinate, which is cleaved by argininosuccinate lyase to arginine and fumarate. Through fumarate, the arginine conversion cycle and NO formation are linked to the tricarboxylic acid cycle. Arginine is used in cells to synthesise not only NO, but also proteins, urea, creatinine, polyamines, proline, and glutamate [10]. Arginine is involved in a number of biological processes, being the basis of many reactions for the synthesis of other amino acids, as well as a substrate for two enzymes: nitric oxide synthase (NOS) and arginase, which are essential for the formation of NO and urea, respectively.



Citrulline formula



Arginine formula

The definition of «nitric oxide» refers to the reduced form of NO with a half-life from 2 to 30 s [11, 12]. Its stable final metabolites are nitrite (NO_2^-) and nitrate (NO_3^-). Total indicator (nitrite and nitrate) is a product of NO, which is an indirect marker of nitric oxide concentration in the body. In body fluids, including plasma, most nitrite is converted to nitrate [13].

The nitric oxide synthase family includes endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). These NOS isoforms catalyse the conversion of arginine and L-homoarginine to NO, one of the most potent physiological vasodilators and inhibitors of platelet aggregation [14]. NO and other endothelial substances including prostacyclin (vasodilator) and endothelin (vasoconstrictor) have been revealed to play important roles in cardiovascular physiology and pathology [15]. Altered endothelial NO homeostasis as a result of endothelial dysfunction has been revealed to lead to cardiovascular diseases [16].

NO is synthesised from arginine by the enzyme NOS in a reaction involving electron transfer from nicotine amide adenine dinucleotide phosphate (NADP) – via flavinadenine dinucleotide and flavinmononucleotide in the C-terminal reductase domain – to heme in the N-terminal oxygenase domain, where the substrate arginine is oxidised to citrulline and NO [17]. The formation of NO occurs in two steps. First, NOS hydroxylates arginine to Nω-hydroxy-arginine (which remains largely bound to the enzyme). NOS then oxidises Nω-hydroxyarginine to citrulline and NO [18]. Under normal conditions, NOS catalyses the conversion of arginine, O_2 and NADPH electrons into NO and citrulline. However, in the presence of pathological conditions such as atherosclerosis and diabetes mellitus, NOS function is altered and the enzyme catalyses the reduction of O_2 to superoxide (O_2^-), a phenomenon commonly referred to as «NOS uncoupling» [19, 20].

2. THE ROLE OF ARGININE IN PATHOLOGY

One of the main mechanisms for the development of PAH is endothelial dysfunction [21-23]. In addition to PAH, it plays a role in the development of other diseases, including diabetes, atherosclerosis, and others. More importantly, many authors have revealed that the systemic manifestations observed in COVID-19 can be explained by endothelial dysfunction [24-26]. Actually, alterations in endothelial function have been associated with hypertension, diabetes mellitus, thromboembolism and renal failure, which have been observed to varying degrees in COVID-19 patients [27-30]. H.M. Al-Kuraishy, et al. [31] revealed that due to antiviral and immunomodulatory effects, L-arginine and released NO have interrelated effects against SARS-CoV-2 infection.

Over recent years, there has been growing interest in the potential therapeutic effects of arginine supplementation, especially in cardiovascular disease. Disruption of NO synthesis is considered a major sign of endothelial dysfunction [32]. Concurrently, some authors have revealed that arginine intake in healthy subjects does not significantly increase NO production [33]. For instance, daily administration of citrulline or arginine during 8 days to 15 well-trained swimmers had no effect on serum NO concentration, nor did it improve their performance at 100 and 200 m [34].

That said, other studies reveal the positive effects of arginine supplementation in healthy individuals. For example, arginine supplements have been tested on athletes because vascular dilation promotes oxygen perfusion during exercise, enhancing muscle strength and recovery [35]. These studies have produced conflicting results, sometimes finding no effect of arginine supplementation over physical performance and sometimes finding a significant improvement in exercise tolerance [36, 37].

The paradox of arginine is that although its intracellular physiological concentrations are only a few hundred micromoles per litre, thus exceeding the Km of eNOS, acute administration of exogenous arginine further increases NO production [38]. One mechanism that may help explain the arginine paradox is related to the discovery of asymmetric dimethylarginine (ADMA), an endogenous NOS inhibitor [39].

Symmetric dimethylarginine (SDMA) is not a NOS inhibitor, but can indirectly reduce NO production through competitive interaction with cellular L-arginine [40]. SDMA is a methylated arginine amino acid. SDMA, together with its biologically active structural isomer ADMA, is formed as a consequence of intranuclear methylation of L-arginine residues of various regulatory proteins and is released into the cytoplasm after proteolysis. SDMA is excreted by the kidneys, while ADMA is largely metabolized [41].

Increased ADMA concentrations have been revealed in hypertension in experimental animals [42, 43]. An increase in ADMA concentration was recorded with PAH. Thus, in children aged 12–17 years, this index was observed to increase to 0.640 ± 0.017 μmol/l, which was statistically significantly ($p < 0.01$) higher than the level of the control group – 0.27 ± 0.02 μmol/l [44]. In paediatric PAH, ADMA levels were directly correlated with beta-salusin, but no relationship between beta-salusin and SDMA was revealed [45]. A cross-sectional study involving school children aged 6–9 years from the Eastern Cape Province of South Africa revealed a direct correlation between obesity, hypertension and ADMA [46].

V.I. Podzolkov et al. revealed a statistically significant increase in ADMA concentration in patients with essential arterial hypertension compared to physiological norm. Moreover, this increase was greater in the group with uncontrolled AH (UAH) compared to controlled AH (CAH). In intergroup analysis among patients with UAH, there was a significant positive correlation between ADMA concentration and creatinine level ($r = 0.615$; $p < 0.05$), and a statistically significant

negative correlation between ADMA level and renal filtration function assessed using the glomerular filtration rate (r = -0.444; $p < 0.05$). With increasing levels of ADMA in serum, a statistically significant decrease in glomerular filtration rate was observed ($p < 0.05$). Also, a statistically significant positive correlation between ADMA content and progression of brachiocephalic artery stenosis was revealed in the group of patients with UAH ($r = 0.5$; $p < 0.05$). The authors believe that statistically significant correlation between ADMA level in patients with UAH and parameters of renal function decline and progression of brachiocephalic artery stenosis indicates the potential use of arginine as a marker of target organ damage and prognosis of the disease course [47].

Considering its similar structure to arginine, ADMA is a direct competitor for NOS binding. More importantly, both ADMA and arginine are transported into the cell via a highly affinity Na+-independent carrier of basic amino acids [48], and therefore also compete with each other at this level. Since ADMA competes with arginine for NOS and cellular transport, NO bioavailability depends on the balance between the both.

Arginine administration can balance the arginine/ADMA ratio, restoring NO production. The increased availability of arginine as a result of ingestion, in other words, competes with ADMA in binding eNOS. This interesting mechanism sheds light into the efficacy of increased arginine availability, suggesting its further therapeutic potential [49].

3. DISRUPTION OF NO PRODUCTION AS A MECHANISM OF ENDOTHELIAL DYSFUNCTION AND ARGININE INTERVENTION

The ability of the endothelium as a regulator of vascular homeostasis is largely dependent on NO production, making insufficiency of endothelial vasodilators a major sign of endothelial dysfunction. The impaired endothelial availability of NO in the vascular network may be associated with decreased NO synthesis or, indirectly, with increased production of reactive oxygen intermediates (ROIs), which inactivates the NO source [50]. In addition to counteracting oxidative stress, stimulation of NO synthesis represents an alternative and potentially effective approach, for example by providing additional substrates to NO synthase. Arginine supplementation theoretically fulfils these needs and therefore they have been tested in many cardiovascular diseases as a potential therapeutic strategy [51]. Studies examining the use of arginine on humans, however, have often been controversial. Actually, in healthy individuals as well as in patients with cardiovascular disease, plasma arginine levels range from ~45 to ~100 μmol/L [52], which is significantly higher than the eNOS Km of 2.9 μmol/L. Endocrine mechanisms may also contribute to arginine-induced vasodilation. In fact, arginine stimulates the release of insulin and glucagon by pancreatic islets of Langerhans [53].

Numerous data indicate that endothelial dysfunction is common in many diseases. A.A. Khan et al. revealed it in atrial fibrillation and associated a high risk of complications with endothelial dysfunction [54]. Endothelial dysfunction and C-reactive protein predict the incidence of heart failure in patients with arterial hypertension [55]. Endothelial dysfunction is also associated with age-related decline in cognitive and physical function [56], as well as with the pathogenesis of stroke [57], diabetes mellitus [58], erectile dysfunction [59] and heart failure [60].

Clinical studies examining the effects of arginine against endothelial dysfunction caused by aging have yielded conflicting results. Acute intravenous infusion of arginine (1 g/min for 30 min) had no effect on endothelial-dependent vasodilation in healthy elderly subjects [61]. However, intravenous arginine administration caused a significant increase in renal plasma flow, glomerular filtration rate, natriuresis and potassauresis in young but not in elderly hypertensive patients [62].

4. ARGININE INTAKE IN HYPERTENSION

Most studies in animal models have confirmed the beneficial effects of citrulline and arginine supplementation in elevated BP. The arginase pathway is responsible for the catabolism of 76–85 % and 81–96 % of arginine in the extraintestinal tissues of pigs and rats, respectively. Arginine supplementation (315 and 630 mg Arg/(kg body weight per day) for 91 days) had no adverse effects on male and female pigs. Similarly, no safety concerns were observed in male or female rats supplemented with 1.8 and 3.6 g arginine/(kg body weight per day) for at least 91 days. Intravenous administration of Arg-HCl to pregnant ewes at doses of 81 and 180 mg Arg/(kg body weight per day) is safe for at least 82 and 40 days, respectively. Animals receiving a normal diet can tolerate large amounts of Arg (up to 630 mg Arg/(kg body weight per day) for pigs or 3.6 g Arg/(kg body weight per day) for rats) well for 91 days, equivalent to 573 mg Arg/(kg body weight per day) for humans. Collectively, these results may help in studies to determine the safety of long-term oral administration of Arg in humans [63].

Brazilian authors have assessed whether endothelial function of vertebral arteries (VA) is impaired in men with hypertension. In 13 men with arterial hypertension (46 ± 3 years) and 8 men from the control group of the same age (46 ± 4 years), BP (photoplethysmography), blood flow in the vertebral (VA) and common carotid artery (CCA) was determined by duplex ultrasound. Results were recorded at rest and within 30 min after intravenous injection of L-arginine (30 g) or isotonic solution. The control group and hypertensive patients demonstrated similar blood flow at rest (601 ± 30 ml/min vs. 570 ± 43 ml/min in controls; $p = 0.529$) and blood flow in VA (119 ± 11 ml/min vs. 112 ± 9 ml/min in controls; $p = 0.878$). During L-arginine administration, blood

flow in the CCA increased equally between groups (12 ± 3 % in the group with AH and 13 ± 2 % in the control group; p = 0.920). In contrast, increased blood flow in VA was absent in subjects with hypertension (0.8 ± 3 % compared with controls, 16 ± 4 %; p = 0.015) without significant change in BP. Flows in both CCA and VA returned to near resting values within 30 minutes after infusion, and four patients with hypertension and three of the control group had no significant effect on blood flow in VA or CCA. The results demonstrate endothelial dysfunction in the posterior cerebral circulation in middle-aged men with arterial hypertension [64].

Iranian authors studied the effect of L-arginine supplementation over BP by conducting a systematic review and meta-analysis of dose-effect relationships in randomised placebo-controlled clinical trials (RCTs). They searched online databases for relevant keywords up to April 2021 to identify RCTs using oral L-arginine supplementation to measure systolic BP (SBP) and diastolic BP (DBP) in adults. Inclusion criteria were adult participants and duration of intervention ≥ 4 days. Exclusion criteria were L-arginine infusions and emergency interventions. A random effects model was used to estimate the weighted mean difference (WMD) and 95% confidence interval (95% CI). 22 RCTs were included in this meta-analysis. Pooled analysis demonstrated significant reductions in SBP (WMD = -6.40 mmHg; 95% CI: -8.74; -4.05; p < 0.001) and DBP (WMD = -2.64 mmHg; 95% CI: -3.94; -1.40; p < 0.001) after L-arginine supplementation. Subgroup analyses showed significant reductions in SBP and DBP regardless of baseline BP category (normotensive, hypertensive), study duration (≤ 24 days, > 24 days), sex (female, male), health status (healthy, unhealthy), and body mass index (normal, overweight, obese). No significant changes were observed at doses > 9 g/day, trial duration > 24 days, or in obese subjects. L-arginine supplementation also reduces DBP more effectively in women than in men. Moreover, meta-regression analysis of DBP demonstrated a significant association between the dose of L-arginine intake and DBP changes (p = 0.020). In non-linear dose-response analysis, the effective dose of L-arginine was found to be ≥ 4 g/day for SBP (p = 0.034) regardless of study duration. Overall, the authors believe that L-arginine supplementation may be effective in reducing BP [65].

Chinese authors have examined the effects of traffic-related air pollution over BP, cardiovascular disease, and mortality. They aimed to assess the potential efficacy of L-arginine supplementation in mitigating adverse cardiovascular effects in adults with elevated BP while walking outdoors under conditions of vehicular air pollution using a randomised, double-blind, placebo-controlled trial. A total of 118 adults with elevated BP were enrolled and randomly assigned to either a placebo group or an intervention group with L-arginine supplementation at a dose of 9 g/day for 2 weeks. On day 14, participants from the two groups walked in pairs along the carriageway for 2 hours. Resting BP, L-arginine nitric oxide metabolites, and inflammatory biomarkers were measured before, during, and after a 2-hour exposure, and BP measurement and Holter monitoring were performed during a 2-hour outdoor walk. Participants in the main group had significantly increased plasma L-arginine levels compared to the placebo group after supplementation. Both groups were exposed to the same traffic-related air pollutants. However, participants in the main group revealed a significant decrease of 5.3 mmHg (95% CI: -9.9; -0.7) in resting SBP, 4.3 mmHg – in resting DBP, and 4.6 mmHg (95% CI: -7.9; -1.3) in resting mean blood pressure (mBP) at 30 minutes after a 2-hour outdoor walk compared with the placebo group. There were also significant reductions in ambulatory SBP, DBP, and mBP (7.5–9.9 mmHg, 5.3–7.6 mmHg, and 4.7–7.9 mmHg, respectively) during walking in the main group compared with the placebo group. No significant changes in ST segment levels, L-arginine (NO) metabolites and inflammatory biomarkers were revealed, and no statistically significant associations were observed between specific traffic-related air pollutants and measures of cardiovascular health. The study reveals that oral L-arginine supplementation was safe and well tolerated, and could improve BP levels in adults with elevated BP while walking in the air, even when it was polluted due to traffic [66]. Other authors also reveal a favourable effect of arginine supplementation on the course of PAH [67-69].

CONCLUSION

In summary, the amino acid arginine is a molecule involved in BP regulation. Asymmetric dimethylarginine and its structural isomer, symmetric dimethylarginine, are predictors of the development of a complicated course of cardiovascular disease. Previous studies conducted in relation to the therapeutic use of arginine are contradictory, making it difficult to put the results into practice.

Overall, the literature data recommend arginine supplementation for cardiovascular disease, especially to prevent the development of hypertension and atherosclerosis. One of the limitations of arginine supplementation remains the selection of the optimal target group. With respect to these concerns, we believe that ADMA levels can be very useful in selecting a target population, and patients with an elevated ADMA/arginine ratio are probably the most appropriate group for whom arginine supplementation may indeed be effective. Another limitation to the use of arginine concerns its dosage. Indeed, the available evidence offers a range of different doses – sometimes effective, sometimes not. Unfortunately, much of the evidence about the effects of arginine with regard to hypertension comes from small clinical trials, and despite the promising efficacy, further, especially large, randomised and controlled trials are needed.

Conflict of interest

The authors of this article declare no conflicts of interest.

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