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Does L-arginine supplementation play a role in cerebral small vessels disease? Implication in the treatment of leukoaraiosis

R.S. Calabrò *, G. Gervasi, P. Bramanti

IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy

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ABSTRACT

Although leukoaraiosis can be considered as a part of the normal aging process, it is strongly associated with stroke, cognitive impairment and other disabilities. The pathogenesis of leukoaraiosis is poorly understood, even if chronic ischemia with consequent arteriolosclerosis probably due to endothelial dysfunction has been suggested. To date, treatment focuses only on prevention of lesion formation and progression by aggressive control of risk factors, beginning at an early age and continuing throughout life.

L-Arginine, a semi-essential amino acid, is a precursor of NO in the reaction catalyzed by endothelial nitric oxide synthase and, it has been recently found to importantly influence endothelial function. Arginine supplementation has been demonstrated to be safe and effective therapy for many health conditions, particularly vascular diseases such as intermittent claudication, angina pectoris, erectile dysfunction and MELAS.

Thus we hypothesize that, since a lack of endothelium-derived NO may be responsible for several features of LA, long-term administration of high oral doses of L-Arg may slow LA progression and the associated functional impairment.

Introduction

L-Arginine, a semi-essential cationic amino acid (CAA) involved in multiple areas of human physiology and metabolism, is a precursor of nitric oxide (NO) in the reaction catalyzed by endothelial nitric oxide synthase (NOS) and, recently, it has been found to crucially influence endothelial function [1]. Supplementation with L-Arg was demonstrated to retard, halt or reverse atherogenesis in experimental animal models. Therefore, many clinical studies in which L-Arg was used to improve symptoms of vascular disease have been performed, leading to controversial results [2,3].

However, arginine appears to be safe and effective therapy for many health conditions, particularly vascular diseases responsive to modulation of endothelial-derived relaxing factor including intermittent claudication, angina pectoris and erectile dysfunction [4].

From the different doses and routes of administration that have been used in these studies, it is possible to conclude that the effects of L-Arg and the underlying mechanisms vary according to the plasma concentration that is reached [3,4].

Interestingly, a recent study showed that after oral L-arginine supplementation in mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) the frequency and severity of clinical symptoms caused by stroke were dramatically decreased without any serious adverse events [5]. Moreover, L-arginine was suggested to improve the segmental impairment of intracerebral arterial vasodilatation in patients with MELAS, which often present a decreased vasodilatation capacity of the small arteries. This vasodilatatory impairment is determined by accumulation of free radicals and/or superoxides – whose increasing is due to MELAS defective respiratory chain activities – and asymmetrical dimethyl-arginine (ADMA), and leads to NO synthase reduction and endothelium dysfunction with consequent cerebral ischemia [6].

With the widespread clinical use of magnetic resonance imaging of the brain, areas of altered signal intensity are frequently identified in the periventricular and subcortical white matter of elderly persons [7]. A term commonly used to describe these radiographic lesions is leukoaraiosis (LA), which comes from the Greek *leukos* (white) and *araiosis* (rarefaction), signifying a decrease in density of white matter. Traditionally these brain findings have been considered without clinical relevance since many affected individuals are asymptomatic. Nevertheless, accumulating research shows an association of LA progression with increased risk of stroke, gait impairment and cognitive decline [8–13].

Although LA pathogenesis is still not well understood, mounting evidence suggests a pivotal role of a chronic ischemic injury due to the arteriolosclerosis of penetrating end arterioles [14]. Arteriolosclerosis is considered to be predominantly secondary to endothelial

* Corresponding author. Address: IRCCS Centro Neurolesi "Bonino-Pulejo", S.S.113 Via Palermo, Cda Casazza, 98124 Messina, Italy. Tel.: +39 090 6012937; fax: +39 090 6012850.

E-mail addresses: salbro77@tiscali.it, roccos.calabro@centroneurolesi.it (R.S. Calabrò).

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dysfunction, even if a possible oxygen trafficking system and neurocellular energy pathways involvement can not be ruled out [15]. Moreover, the role of blood–brain barrier in preventing the progression of LA has been hypothesized [16], and a potential influence of some candidate genes (i.e., polymorphic variation in the gene encoding angiotensin-converting enzyme and the apoprotein-E) to susceptibility for LA was supposed [17].

However, since endothelium-derived NO has a number of roles including maintaining basal cerebral blood flow, cerebral vasodilatation, autoregulation and vascular integrity and inhibiting smooth muscle cells proliferation [18], a lack of endothelium-derived NO would be expected to lead to several features of LA.

Treatment of LA is empirical and, to date, focuses on prevention of lesion formation and progression by aggressive control of vascular risk factors (arterial hypertension, dyslipidemia, diabetes mellitus, heart diseases, smoking, alcohol consumption and hyperhomocysteinemia) beginning at an early age and continuing throughout life [19]. Antithrombotic agents may represent an important component in prevention while the effectiveness of carotid endarterectomy in patients with severe carotid artery stenosis decelerating the progression of LA has not yet showed, even if some results suggest possible benefits [20]. Among the few small therapy trials in LA patients, one pilot study found positive effect of nicergoline on cognitive function [21]. Similarly, a small-size open trial demonstrated that nimodipine, when chronically administered in patients with LA, was safe and had beneficial effect on cognitive functions [22].

The hypothesis

The hypothesis we suggest here is whether long-term administration of high oral doses of L-Arg may slow LA progression and whether LA-related functional disability may benefit from this treatment. Indeed, although L-arginine could restore the impaired endothelial function and seems to be somehow effective in different vascular diseases [3], to our knowledge, no prospective studies have been performed so far to evaluate its effectiveness in cerebral small vessel disease, such as LA. The effects of L-arginine supplementation on human physiology appear to be multicausal and dose related. Doses of 3–8 g/day appear to be safe and not to cause acute pharmacological effects in humans [23].

The theory of our hypothesis

A promising effect of high dose L-Arg administration in LA may be due to the increased production of NO causing vascular dilatation and neuronal plasticity.

NO synthesis is mainly mediated by the balance of two cytoplasmatic enzymes: NOS and L-arginase. NOS produces NO and N^G-hydroxyl-L-arginine from L-arginine and O_2. L-arginase, whose V_{MAX} is 1000 times greater than those of NOS, may compete with NOS for L-arginine utilization to yield urea and ornithine. Arginase activity is inhibited by N^G-hydroxyl-L-arginine concentration.

L-Arg metabolism is complex, since it serves as storage of nitric compounds such as nitrite and nitrate. Arginine metabolism is diverse in the different human tissues and organs. The main pathways of arginine metabolism in the nervous system are NO synthesis or arginine inclusion into proteins. Brain arginine is derived from blood or protein breakdown. De novo synthesis of arginine from ornithine does not concern neural cells. As arginine is important in the brain for NO formation, diet supplementation of Arg in the elderly is required when its blood concentration is lacking. Proteins breakdown in aged brain produces arginine analogs, such as N^G-monomethyl-arginine (NMMA) and ADMA, which may compete with arginine in different pathways [1]. Moreover, decarboxylation produces the polyamine agmatine, which has been recently identified as a signaling molecule in nervous system. NMMA, ADMA and agmatine are considered physiologic inhibitors of NOS activity in human tissues. However, high dose L-Arg seems to restore inhibited NOS activity eliminating this physiologic inhibition [24,25]. Interestingly, high dose of oral L-Arg supplementation are successfully utilized in several inherited diseases in which arginine's cycle enzymes are lacking. Indeed, this diet supplementation seems to improve metabolic, physical and cognitive impairment of the affected individuals [2].

NO is considered as the most important endothelial vasodilatator produced by endothelial cells (eNOS). Beside eNOS, another NOS isoform (neuronal NOS or nNOS), whose activity is still unclear, has been isolated from human brain tissue.

Nevertheless, a possible involvement of nNOS activity in neurotransmitter regulation including glutamine, acetylcholine, dopamine, γ-aminobutyric acid and bombesin, and in memory formation, cerebral vascular tone maintenance, and systemic blood pressure and flow control has been lately demonstrated. Moreover, also the nNOS-derived NO seems to act on local vascular smooth muscle relaxation. As showed in anesthetized phentolamine-treated dogs [26], about two-thirds of cerebral vasodilatation is mediated by nitrergic vasomotor center, which provide periarteriolar vasodilatatory nerves. Under physiological condition, in which cerebral arteries are constricted, blood flow is controlled mainly by different degrees of vasodilatatory system activity. The brain vasculature's tone is mostly due to transmural pressure, circulating vasoconstrictors, and weakly to the adrenergic nerve activity. On the contrary, it is well recognized that peripheral vascular tone, with the exception of coronary arteries, is largely regulated by the adrenergic system activity. Thus, vasodilatation appears to be mainly induced by a decrease in adrenergic activity and an increase in nitrergic nerve activity [27].

Since LA is thought to be characterized by chronic ischemia due to endothelium dysfunction, treatment with L-arginine may restore the normal NO extracellular fluid concentration necessary to basal cerebral blood flow. Furthermore, L-arginine effect on neurotransmitter regulation of central nervous system could delay the degenerating process of LA slowing and/or improving patients' typical cognitive and motor impairment.

Unfortunately, high doses of L-arginine are required to ensure a right production of NO into the brain. As other CAA, L-arginine trespass the blood–brain barrier via specific system y^+ transfer. Although system y+ was detected only in the luminal (blood side) membrane, no detectable Na+-dependent transport system similar to anionic amino acids one was found for CAA in the abluminal (brain side) membrane. O'Kane et al. [28] have recently supposed that arginine flux through brain–blood barrier is mainly mediated by combined electrical and chemical driving force. Assuming cerebral spinal fluid concentrations of L-arginine is 10–30% of those in plasma, the net movement of L-arginine would occur from plasma to brain especially in the presence of high blood concentration of L-arginine.

This is the reason why we suggest long term and high dose L-arginine supplementation to maintain and/or improve a proper deep brain circulation preventing chronic ischemia.

Consequences of the hypothesis and discussion

Over the last years, evidence on prevalence, clinical significance and prognostic value of LA has been dramatically mounting. Nowadays we know that minimal changes are frequently found in general population and data are sufficient to sustain that the mildest degree of LA can be considered as an almost normal finding

in the brain of elderly patients. In contrast, moderate to severe LA are not so benign and are correlated with motor and gait impairment, depressive symptoms, urinary disturbances and cognitive deficits [8,11,29,30].

Longitudinal studies have demonstrated a predictive role of LA in terms of less favorable prognosis in the general population and in a number of clinical conditions.

In fact the presence of LA is associated to an increased risk of ischemic stroke, dementia, vascular mortality, bleeding in patients on anticoagulation or undergoing cerebral thrombolysis and carotid artery surgery [31–34]. The multicenter Leukoaraiosis and Disability in the Elderly Study (LADIS) has assessed the role of age-related white matter lesions as an independent predictor of the transition to disability in initially non-disabled elderly people showing that LA and lacunar infarcts are independently associated with cognitive decline [13,29,35].

Life expectancy has increased substantially in last 50 years all over the world. The pattern of disease is also shifting from acute communicable to chronic non-communicable ones. Such diseases, mainly involving central nervous system, lead to a lot of disability. More and more people with disability continue to survive as compared to previous times leading to an important increase of costs in healthcare.

Because its high prevalence in individuals aged over 65, LA-related disability has a relevant socioeconomic burden and its prevention and/or slowing of progression could significantly reduce healthcare costs and improve patient quality of life.

Thus, this hypothesis, focusing on a possible efficacy of high dose L-arginine on prevention and/or treatment of LA, could have important public health implications as LA increases the overall vascular morbidity and mortality enhancing the risk of stroke and dementia.

Conflict of interest

The authors have no conflict of interest.

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