ISSN: 2586-7342 © 2019 KFHCA. http://www.kjfhc.or.kr
doi: http://dx.doi.org/10.13106/kjfhc.2019.vol5.no4.25.

L- Arginine as a dietary supplement and its role in protection from disease and metabolism

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Received: May 07, 2019. Revised: May 08, 2019. Accepted: July 02, 2019.

Abstract

Now a days problem in health has become common. So, instead of curing them, prevention through dietary supplements has proven to be useful. In the case of patients who have already developed the disease atleast relieving pain and suffer is a challenging thing. In this context L- arginine is doing better compared to other essential aminoacids up to some extent. Arginine was found to reduce the pain associated with pulmonary hypertension foun to be associated with sickle cell anaemia. It also reduces the reperfusion injury after ischemia, trauma and shock. Some of the drugs with L-arginine as component are under clinical trials and hope to be available in the market soon. Severe preeclampsia is characterised by headaches, blurred vision, and inability to have high photovision, nausea and vomiting. L-Arginine along with Vit C and E are given as medical food to the patients and decrease in condition symptoms is the project now under phase II clinical trial. However the role of arginine in ameolirating preeclampsia symptoms is uncertain except with that of hypertension. Arginine is used to treat pain in sickle cell anaemia, lung damage, reperfusion injury, Trauma and shock but should be excluded during sepsis.

Keywords: Sickle Cell anaemia, L- Arginine, Ischemia, Glutamate, Vasodilation, Nitric oxide

Major classification: Health Science.

1. Introduction

Arginine is one of the basic aminoacid found to be associated with histones and also one of the essential aminoacids now. Arginine is provided by diet, and also found to be synthesised in the body through intestinal-renal axis. Glutamate supplied through diet acts as precursor for arginine by providing the nitrogen group and reduction of carbonyl group leading to formation of citrulline. In kidney it is converted to arginine. Arginase is the one of the enzyme that converts arginine to ornithine and urea in urea cycle . Arginase is one of the enzyme that is under therapeutic interest due to its effect on arginine bioavailability ratio.

Sickle cell anaemia is one of the diseases due to mutation of single codon that codes for glutamine to valine. As a result of this mutation, the RBC develops sickle shape and unable to tolerate the stress during capillary passage and most of them hemolyse during the passage.The binding capacity of oxygen for Hb present in sickle RBC is less, and also the metabolic waste is not cleared. As a result of this the patient suffers with pain and pulmonary hypertension and lung damage.

Ischemia is the condition where there is occlusion in blood flow due to some damage or deposition of fat. After the treatment of the condition, reperfusion injury results as sudden flow of blood and oxygen generates free radicals. Arginine is one of the aminoacid that prevents reperfusion injury by generation of NO which causes vasodilation. Brain ischemia is very life threatening compared to myocardial ischemia as 5 min complete loss of

blood supply kills the neuron cells where as 20-40min in case of myocardial ischemia and kidney cells (Lee et al., 2000). Arginine also protects from excitated signalling of glutamate, trauma and shock. This review mainly focuss on uses of arginine in various diseases and disorders and metabolism of glutamate to arginine.

2. Arginine and its role in sickle cell anaemia

Arginine is considered as one of the essential aminoacid present in meat, diet, nuts etc., and is required for production of NO by iNOS . NO causes vasodilation during hypertension and arginine is metabolised equally by other enzyme arginase which uses arginine as the substrate and degrades it in to ornithine and urea in urea cycle. Arginine is synthesised in intestinal- renal axis. Arginase is of two types one is cytosolic and the other is mitochondrial specific. Arginase wasfound to be present in red blood cells also, so hemolysis of which leads to release of arginase in to circulation. In certain disease conditions like release of Hb, trauma, inflammation and pulmonary hypertension leads to increase in arginase and decrease in NOS levels. Uncoupling of NOS also leads to synthesis of ROS by superoxide production. In the other direction increased arginase levels in plasma leads to production of ornithine and citrulline which directs the synthesis towards polyamines and endothelial proliferation which leads to pulmonary hypertension and also asthma.

Sickle cell anaemia is present most commonly in African Americans but it is recognised as disease of orphans and found in less than 200,000 individuals. Arginine is one the FDA approved drug to sickle cell anaemia and Morris and her colleagues proposed arginine bioavailability ratio which indicates the ornithine levels, Plasma arginine levels, Production levels of NO and arginase degradation of arginine. But she also stated that patient selection is important as who suffers sepsis should not given with arginine and patients who has sickle cell anaemia without sepsis is preferable for oral intake of drug arginine.

Glutamine acts as prodrug for arginine and given to restore arginine levels and the pathway of arginine in sickle cell anaemic patients is uncertain but as morris said it may be due to reduction in free radical production through NADPH. Arginine is also required for Naïve T- cell activation, as loss of which leads to ablation of memory response and T- cell cytotoxicity. Arginine also reduces the pain associated with sickle cell anaemia by preventing pulmonary hypertension and lung trauma. Glyceraldehyde dehydrogenase serves as marker for sickle cell anaemia as it is a marker for hemolysis and PRMT5 is one of the enzyme found in sickle anaemia which methylates arginine of histones and also prevents switching of ɤ- globlin during fetal stage to adult stage.

2.2. What causes pain in sickle cell anaemia

Epithelial cells lines entire systems of the body and controls Nitric oxide production. NO is required for the free passage of red blood cells through the capillary and whenever the RBC signals the epithelial cells they synthesises the NO from L- arginine and releases it in to the blood. So, the RBC movement is possible and also removal of metabolic waste and toxic products from the cells is possible through exchange and release of Oxygen. In sickle cell anaemia NO levels are low due to low arginine availability. So, RBC are unable to pass through capillaries and hemolyse due to reduced elasticity and reduced oxygen availability, which leads to lactic acid production which causes irritation in the tissues and finally the pain.

2.3. How glutamine converts in to citrulline and arginine

Glutamine contributes 6^{th} nitrogen group in citrulline but which component contributes the carbonyl amine at 7,8 th positions of citrulline is not known and reduction of carbonyl group to methylene group occurs in citrulline at 5^{th} position in the intestine and released in to circulation and in renal tissue citrulline is converted to arginine.

2.4. How arginine activates Naïve T cell

When T- cell get activated by presentation of antigen, rise in arginine levels are observed. As activation of T-cells causes shift from glycolysis to oxidative phosphorylation the arginine levels are lowered due to requiring needs of substrates like α- Ketoglutarate due to the anaplerotic reactions. Arginine also participates in various signalling pathways and G- protein coupled receptor activation in macrophages along with production of NO and upregulation of proinflammatory genes.

3. Metabolism of L- Arginine in sickle cell anaemia

In sickle anaemia as from previous reports arginine is metabolised in to asymmetric and symmetric dimethyl arginine and N- monomethyl arginine (Kato et al., 2006). As already discussed PRMT5 is a gene that expressed in sickle cell traits which may cause
methylation of arginine in to above metabolites inhibiting the production of NO.

3.1. Role of arginine in trauma and shock

NO synthesised from arginine regulates vascular tone of the endothelium and is required for recovery of the tissue after trauma. Arginine prevents the infiltration of neutrophils in liver may be by preventing the secretion of inflammatory chemokines and inhibition of chemokine signalling. Arginine also protects the cerebral hemisphere of the brain from ischemic injury even at low dosage by preventing the excitated activity of glutamate (Kondoh et al., 2010). Glutamate binds to four types of receptors like AMPA, NMDA, kainite and metabotropic in which first three are ionotropic and voltage gated but metabotropic receptors are G- coupled receptors. As already there are reports that arginine binds to G- coupled receptors and inhibits the signalling by glutamate, which has yet to be proved. Lysine also protects from ischemia but relatively at high dosage than arginine proved by the results of Kondoh et al., (2010).

3.2. Diet supplementation during Ischemia

Grape powder supplementation resulted in decrease in glial cell activation, delayed neuronal death and apoptosis in neuronal cells (Wang et al., 2005). This is due to polyphenol content of grape powder which provides antioxidant requirement to reduce the free radical induced damage in the brain. Arginine also now known to increase the serum total antioxidant capacity but has no effect on enzymes like glutathione peroxidise and superoxide dismutase in case of obese patients with pre diabetes (Fazelian et al., 2014). According to National stroke association, diet rich in antioxidants like fruits and vegetables should be consumed more and diet low in cholesterol and salt should be taken to prevent next stroke occurrence.

Dietary supplements can be given to patients with cystic fibrosis, insulin resist ance and diabetes (McNeal et al., 2016). L-Arginine supplement as drug was under clinical trials in order to treat moderate to severe asthma. The organisations funding this research are NIH and National Center for Research and Resources Clinicaltrials(2019 a). Similarly Arginine and Vit- C and E are included in medical diet to treat preeclampsia which is the leading cause of maternal mortality and morbidity during third trimester and is in phase II trial. The disease is characterised by life threatening problems like seizures, hepatic dysfunction, renal failure and coagulopathy. The collaborators of this work include University of Pennsylvania and Bill and Melinda Gates Foundation and sponsor for this work is Instituto Nacional de Perinatologia Isidro Espinosa de los Reyes Clinicaltrials(2019 b).

4. Discussion

Arginine as drug was first approved by FDA and has recognised as a excellent dietary supplement for curing diseases like preeclampsia during gestation, diabetes and insulin resistance in obese patients. Preeclampsia is characterised by high blood pressure and proteinuria in gestational period of after 20 weeks. Severe preeclampsia is characterised by headaches, blurred vision, and inability to have high photovision, nausea and vomiting. L-Arginine along with Vit C and E are given as medical food to the patients and decrease in condition symptoms is the project now under phase II clinical trial. However the role of arginine in ameolirating preeclampsia symptoms is uncertain except with that of hypertension.

Arginine is used to treat pain in sickle cell anaemia, lung damage, reperfusion injury, Trauma and shock but should be excluded during sepsis.

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