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Introduction

Arginine is one of the basic amino acid found to be associated with histones and also one of the essential amino acids now. Arginine is provided by diet and also found to be synthesized 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 enzymes that converts arginine to ornithine and urea in urea cycle. Arginase is one of the enzymes that is under therapeutic interest due to its effect on arginine bioavailability ratio.

Sickle cell anaemia is one of the diseases that occurs 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 hemolyze 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 amino acids 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 whereas 20-40 min in case of myocardial ischemia and kidney cells. Arginine also protects from excited signaling of glutamate, trauma and shock. This review mainly focus on uses of arginine in various diseases and disorders and as well as metabolism of glutamate to arginine.

Arginine and its Role in Sickle Cell Anaemia

Arginine is considered as one of the essential amino acid presents in meat, diet, nuts etc., and is required for

ABSTRACT

Now a day’s problem in health has become more 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 at least relieving pain and suffer is a challenging thing. Arginine reduces the pain associated by synthesizing NO and causing vasodilation of blood vessels in sickle cell anaemia. Ornithine is converted to citrulline and finally to arginine through certain metabolic reactions like transamination. Arginine through NO regulates the endothelium of blood vessels and protects against trauma and ischemia. Arginine supplementation along with antioxidants proved to be useful due to additional protection offered during ischemia.

Keywords: Sickle Cell Anaemia, L-Arginine, Ischemia, Glutamate, Vasodilation, Nitric Oxide
production of NO by iNOS. NO causes vasodilation during hypertension and arginine is metabolized equally by other enzyme arginase which uses arginine as the substrate and degrades it in to ornithine and urea in urea cycle. Arginine is synthesized in intestinal-renal axis. Arginase is of two types one is cytosolic and the other is mitochondrial specific. Arginase was found 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 arginine 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 recognized 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 equally important as who suffers with sepsis should not give 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 anemic 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 shutdown 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 enzymes found in sickle anaemia which methylates arginine of histones and also prevents switching of v-globlin during fetal stage to adult stage.

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 synthesize 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 hemolyze due to reduced elasticity and reduced oxygen availability, which leads to lactic acid production which causes causing irritation in the tissues and finally the pain.

How Glutamine Converts in to Citrulline and Arginine

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

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 signaling pathways and G-protein coupled receptor activation in macrophages along with production of NO and upregulation of proinflammatory genes.

Metabolism of L-Arginine in Sickle Cell Anaemia

In sickle anaemia as from previous reports arginine is metabolized in to asymmetric and symmetric dimethyl arginine and N-monomethyl arginine. 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.

Role of Arginine in Trauma and Shock

NO synthesized 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 signaling. Arginine also protects the cerebral hemisphere of the brain from ischemic injury even at low dosage by preventing the excited activity of glutamate. 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 signaling by glutamate, which has yet to be proved. Lysine also protects from ischemia but relatively at high dosage than arginine proved by the results.

Diet during Ischemia

Grape powder supplementation resulted in decrease in glial cell activation, delayed neuronal death and apoptosis in neuronal cells. 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 peroxidase and superoxide dismutase in case of obese patients with pre diabetes. 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 resistance and diabetes. L-Arginine supplement as drug was under clinical trials in order to treat moderate to severe asthma. The organizations funding this research are NIH and National Center for Research and Resources Clinical trials (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 characterized 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 Clinical Trials (2019 b).

Discussion

Arginine as drug was first approved by FDA and has recognized as an excellent dietary supplement for curing diseases like preeclampsia during gestation, diabetes and insulin resistance in obese patients. Preeclampsia is characterized by high blood pressure and proteinuria in gestational period of after 20 weeks. Proteinuria results in oedema as most of the protein is lost in the urine. Calcium intake can prevent the preeclampsia because in improvement of symptoms like osteoporosis. Hypertension during pregnancy may also cause proteinuria in patients. Severe preeclampsia is characterized by headaches, blurred vision and inability to have high photo vision, nausea and vomiting. Neural development is retarded in child in gestation due to gestation which may leads to various diseases like cardiovascular disease, osteoporosis and diabetes. 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 ameliorating 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. Trauma is followed by inflammation the next step of wound healing; arginine decreases the unwanted immune response by decreasing the inflammatory cytokines. Arginine also required for activation of naïve T cells so, it should not be given in overdoses during sepsis of an organ or tissue.

Conclusion

Arginine as an aminoacid was well known but its role in management of pain and trauma proven to be useful. Arginine in high inake can also helpful during pregnancy in order to get rid of preeclampsia. So; arginine as a drug to be expected in future.

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References