MEDDOCS Open Access Publisher

ISSN: 2639-4383

Annals of Cardiology and Vascular Medicine

Open Access | Review Article

Hypoargininemia

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Received: Jul 25, 2024

Accepted: Aug 28, 2024

Published Online: Sep 04, 2024

Journal: Annals of Cardiology and Vascular Medicine

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Introduction

Background: Prematurity is a leading cause of infant morbidity and mortality across the world and has an incidence of about 10% of all pregnancies in the US. Preterm infants account for most of the neonatal deaths and incur a significant cost to the healthcare system. Premature infants have a deficiency of several amino acids due to being unable to synthesize them in vivo. Some non-essential amino acids are also essential for this population, requiring supplementation. It has been postulated that a significant metabolic issue in the preterm infant is a severe deficiency of arginine, initially identified in the late 1970s and thought to play a preventative role in the development of NEC. [1-3]. Preterm infants have a significantly higher requirement for arginine [4], in part because arginine is heavily present in tissue protein and there are numerous pathways for arginine utilization. It also plays a critical role in ammonia detoxification and is a precursor of nitric oxide. Nitric oxide itself has crucial roles as a vasodilator, an immune mediator and [5,6]. Knowledge of arginine biochemistry and nutrition is potentially quite beneficial in optimizing neonatal health and survival. Our paper

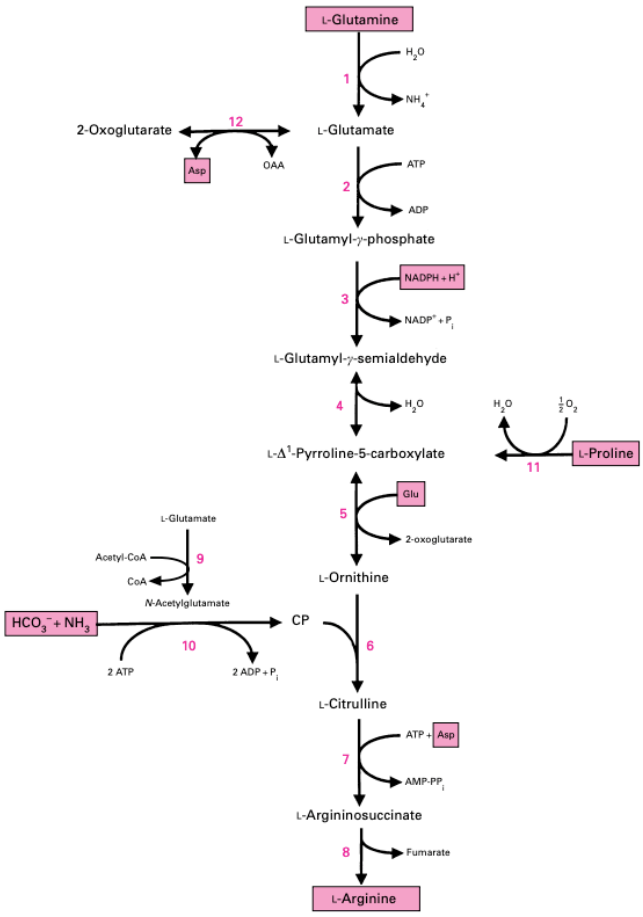

Figure 1: Arginine Synthesis Pathway.

Cite this article: Zainab Makhdoom A, Jain S. Hypoargininemia. Ann Cardiol Vasc Med. 2024; 7(2): 1082.

aims to look at its biochemistry, the current data on its role in prematurity and how it can play a role in minimizing comorbidities of prematurity.

Biochemical pathways

Arginine has been known to play several important functions in physiology and metabolism, as illustrated in animal as well as human studies. Figure 1 illustrates the different pathways involved in arginine synthesis. It is important to note that there is variable expression of these enzymes in different kinds of cells. Most of the enzymes are present in the intestinal mucosa, with some level of expressivity in the liver and kidneys also. However, Pyrroline-5-Carboxylate (P5C) is almost exclusively found in the intestinal tissue.

The enzymes in the pathway depicted above: (1) phosphate-dependent glutaminase (2 & 3) P5C synthetase (4) spontaneous non-enzymatic reaction (5) ornithine aminotransferase (6) ornithine carbamoyltransferase (7) argininosuccinate synthetase (8) argininosuccinate lyase (9) N-acetylglutamate synthase (10) carbamoyl-phosphate synthase I.

Overall, the sources of arginine in the plasma in the fed state can either be exogenous or endogenous. The former refers to arginine that comes from diet and the latter is a result of either de novo arginine production or whole-body protein turnover. Data from Beaumier showed that de novo arginine synthesis accounts for 15% of endogenous arginine flux in adult humans, with the remaining amount arising from whole-body protein turnover. In contrast, data from Flynn and Wu showed that in neonatal pigs de novo arginine synthesis accounted for 30% of endogenous arginine flux. There is a higher percentage of de novo arginine synthesis during the neonatal period because arginine in milk protein is significantly less abundant than in total body protein. It is presumed that this same concept can be applied to human neonates. As a result, neonatal endogenous arginine synthesis is an important regulator of neonatal arginine synthesis [7].

Role of the small intestine

In the small intestine, enterocytes play a significant role in the production of arginine and citrulline from glutamate. This is also evident by the fact that arginine deficiencies result when intestinal citrulline synthesis is prevented by Ornithine Carbamoyl Transferase (OCT) blockers or in individuals who have inherited disorders of OCT defect. Similarly, arginine deficiencies occur if there has been a massive resection of the small intestine. Interestingly, there are developmental changes in this process with time. At birth, the small bowel is predominantly the site for arginine synthesis and over time it becomes the major source of citrulline instead, as the expression of intestinal arginase increases. Arginase is a liver enzyme that hydrolyzes arginine into ornithine and urea. Citrulline is released into the blood from the small intestines and this citrulline is primarily taken up by the kidneys to convert into arginine. Adult intestinal mucosa has increased activity of arginase, and as a result about 40% of the absorbed arginine is degraded through first pass metabolism, and the rest is released into venous blood. Due to arginase significance in arginine breakdown and metabolism it serves as a potential regulatory enzyme in managing the availability of arginine for NO synthesis. There are two isoenzymes of arginase: type I arginase is a cytosolic enzyme located in the liver and type II arginase is a mitochondrial located in the kidney, brain, small intestine, mammary gland, and macrophages with no expression in the liver [7-9].

Renal involvement

The kidney's capacity to synthesize arginine develops overtime. The kidney synthesizes about 60% of the net arginine in adults. This is especially important since the intestinal production of arginine declines with age and the kidneys compensate for this transition. It is in the proximal convoluted tubule that the conversion of citrulline to arginine through Argininosuccinate Synthase (ASS) and Argininosuccinate Lyase (ASL) takes place, after the citrulline is extracted from blood [7].

Role of the liver

The hepatic urea cycle occurring within the periportal hepatocytes is the site of the highest rates of arginine synthesis. It has been shown that hepatocytes can be induced to produce nitric oxide (NO) in response to an inflammatory process. This idea brought into question whether the urea cycle also provided arginine for the synthesis of nitric oxide. Several studies were done to address this question, showing that if the urea cycle does provide any arginine for hepatic NO synthesis, it represents only a tiny fraction of the total arginine synthesized within the urea cycle. They also showed that the hepatic ability to produce arginine is not affected by the presence of stress triggers such as LPS (Lipopolysaccharide) [7].

Although hepatic arginine synthesis is not a major contributor to NO synthesis, the arginine metabolic pathway is a major contributor of NO synthesis in many non-hepatic cells. Arginine plays an important role in NO synthesis by serving as a substrate for nitric oxide synthase (NOS) and as a structural promoter of the dimerization of NOS. Citrulline is co-produced with NO, and can be recycled through the citrulline/NO cycle or the arginine/citrulline cycle shown in Figure 2. This cycle uses the enzymes ASS and ASL which are expressed in almost all cell types [7].

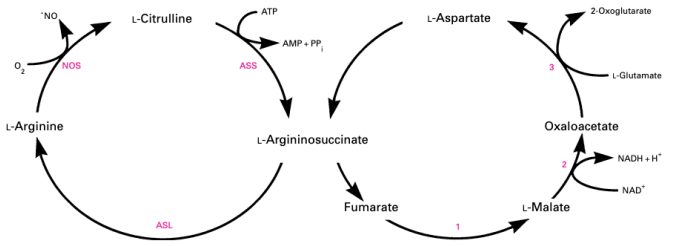

Figure 2: Citrulline/NO or Citrulline/Arginine Cycle.

Significance of arginine in the preterm infant

Preterm infants have relatively immature biochemical systems, including the synthesis of amino acids [10]. Some of these otherwise non-essential amino acids are considered to be essential in this population, making parenteral amino acids administration common practice. Arginine and citrulline are two of these amino acids. Their significance is suggested by the fact that arginine supplementation has been shown to prevent necrotizing enterocolitis (NEC). There have been multiple studies that report lower levels of arginine and citrulline in preterm neonates compared to term neonates. The low levels of both amino acids in this age group suggest that premature neonates are not capable of synthesizing in vivo the amount of arginine that is needed. As a matter of fact, there seems to be a reduced expression of the genes that code for carbamoyl phosphate synthase (CPS-1) Ornithine Carbamoyl Phosphate Transferase (OCT), pyrroline-5-carboxylate reductase (P5CR), Arginosuc-

cinate Synthase (ASS), and arginosuccinate lyase (ASL) 21 in preterm neonates. Additionally, intestinal cells in preterm neonates do not adequately synthesize arginine from its primary precursors glutamate and proline. There are also reports that the glutamate arginine pathway in preterm neonates is non-functional. Moreover, the conversion of arginine to citrulline is also suboptimal in preterm infants, consequently leading to inadequate production of nitric oxide [10-13].

Conclusion

Low plasma arginine concentrations have been reported in neonatal pathologies such as in persistent pulmonary hypertension, necrotizing enterocolitis, and respiratory distress syndrome (14). Arginine is present in lower concentrations in the plasma of the preterm population owing to immature catabolic and anabolic processes. Arginine supplementation may potentially prove to be an important nutritional strategy for preventing and managing diseases associated with prematurity [7]. The significance of arginine from a biochemical standpoint is noticeable in various pathways, just one of which is its role as the precursor of nitric oxide. Nitric oxide has substantial role in our hemodynamics [14].

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