International Journal of Nutritional Sciences

Open Access

Austin Publishing Group

Special Article - Nutrition Diet

Citrulline: Modulation on Protein Synthesis, Intestinal Homeostasis and Antioxidant Status

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Received: June 17, 2019; **Accepted:** July 09, 2019; **Published:** July 16, 2019

Abstract

Citrulline, a nonessential amino acid, is an important precursor substance of arginine. It has been implicated in diverse biological and physiological events, such as nitrogen balance, growth and development, muscle performance, and intestinal homeostasis, but its underlying mechanism in intestinal function is unclear. This review discusses the modulation effects of citrulline on protein synthesis and intestinal homeostasis, as well as its potential mechanisms to broaden its application.

Keywords: Citrulline; Protein synthesis; Intestinal homeostasis; Antioxidant; Nitrogen balance; Gut barrier

Introduction

Citrulline ($C_6H_{13}N_3O_3$), a key intermediate of urea cycle, mainly exist in the watermelon in nature [1]. In mammals, enterocytes have a significant effect on the circulating citrulline levels [2]. Citrulline is essential for various regulation processes, especially during sepsis and endotoxemia [3], and plays an important role in protein synthesis and intestinal homeostasis. Studies have found that citrulline regulates nitrogen balance [4], growth and development [5,6], muscle performance [7], gut barrier function [8-11] intestinal digestion and absorption [12], intestinal cell apoptosis [13] and antioxidant function [4,14,15]. The present review briefly highlights the significant role of citrulline in animals in the modulation of protein synthesis and intestinal homeostasis and points out its potential mechanisms.

Physicochemical property

The term citrulline (Figure 1) was derived from watermelon (*Citrullus vulgaris*) in the 1930s [16]. Citrulline has a molecular weight of 175.19 g/mol and presents two enantiomers, namely, the L and D forms. In nature, citrulline exists in the L form. Under normal temperature and pressure, citrulline is a white crystal or crystalline powder. Citrulline has a melting point of 222 °C and density of 1.289 g/cm [17]. It is well soluble in water but not in ethanol, ether, and methanol [17].

Biosynthesis and Metabolism

Citrulline is synthesized from substrate of arginine, proline, glutamine in the intestine (Figure 2). The common metabolic product of arginine, proline, and glutamine is ornithine, which is then converted to citrulline. The citrulline synthesized by glutamine accounts for the major proportion of the intestinal epithelial cell circulating citrulline levels [18]. The conversion of glutamine to citrulline depends on four enzymes: glutaminase metabolizes glutamine to glutamate, and glutamate regulates the synthesis of pyrroline through Pyrroline-5-Carboxylate Synthase (P5CS). Then, Ornithine Aminotransferase (OAT) converts P5C to ornithine, and Ornithine Carbamoyltransferase (OCT) converts ornithine to citrulline. Arginine converted to n-hydroxy-arginine by the catalysis of Nitric Oxide Synthase (NOS). N-Hydroxy-arginine is then converted to citrulline, and the process releases NO [2,16,18]. Furthermore, arginine can be converted into ornithine by the action of arginase and then into citrulline. Arginase is a key rate-limiting enzyme in the transformation of arginine into ornithine. Proline is metabolized to P5C at first under the action of proline oxidase, then metabolized to ornithine under the action of OAT in the small intestine, liver and kidneys [18]. CO_2 and NH_3 are transferred to citrulline by N-acetylglutamate synthase and Carbamoyl Phosphate Synthase I (CPS-I). The intermediate metabolites are N-acetylglutamate and carbamoyl phosphate [2]. Additionally, in the kidney, citrulline transferred to arginine by ASS and ASL contributes to the majority of endogenous arginine levels [2,17,19]. Citrulline metabolism involves three different pathways: arginine biosynthesis, NO cycle, and complete urea cycle, which take place in the whole body, local sites, liver and kidneys, respectively [16].

Modulation Effects of Citrulline on Protein Synthesis

Citrulline and nitrogen balance

Nitrogen balance is the balance between nitrogen intake and output. It exerts its regulation effects by affecting urea formation. The arginine/glutamine–citrulline cycle contributes to ureagenesis. The liver can absorb arginine and glutamine, activate ureagenesis, and consequently increase amino acid metabolism and protein synthesis. Citrulline synthesis from arginine and glutamine prevents the overactivation of urea formation, thus maintaining the nitrogen balance.

Citrulline is crucial for keeping nitrogen homeostasis. In the absence of arginine supplementation, the concentration of plasma arginine does not decrease, and the plasma citrulline concentration is increased [20]. Citrulline treatment, but not arginine supplementation,

Citation: Xu XM, Wu CM, Jia G, Zhao H, Chen XL, Wang J, et al. Citrulline: Modulation on Protein Synthesis, Intestinal Homeostasis and Antioxidant Status. Int J Nutr Sci. 2019; 4(2): 1033.

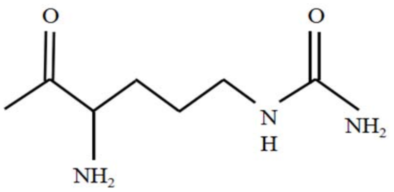

Figure 1: Citrulline structure [16].

increases the concentration of plasma arginine in horses [21] and restores the production of NO in small intestinal cells and the nitrogen balance [3,22-25]. Citrulline supplementation improves the activity and expression of kidney arginine succinate synthase and arginine concentration [12]. This arginine–citrulline cycle is a mean to protect dietary arginine from excessive liver degradation. Moreover, in a mouse model fed with an arginine-free diet, ornithine contributes to citrulline synthesis [26] and ornithine synthesis from citrulline in the small intestinal mucosa of mice [27]. After citrulline is synthesized from ornithine by enterocytes, it is then largely absorbed by the kidneys [28]. In the kidney, almost all the citrulline is metabolized to produce arginine under the action of argininosuccinate synthetase and argininosuccinate lyase. In conclusion, the arginine–ornithine–citrulline cycle is central to maintaining nitrogen homeostasis.

Citrulline and growth

Animal growth and development is the guarantee of efficient production, which is influenced by many factors, such as animal species, nutrition level, environment and maternal effect [29-31]. Citrulline supplementation is an important nutrition regulator in animal growth and development. In the cases of intrauterine growth restriction, the supply of citrulline promotes fetal development. Fetal growth enhancement is related to increased fetal muscle protein synthesis [5,6]. This promotion effect may also be related to increased hormone secretion. Citrulline contributes to the release of a variety of endocrine hormones, mainly including the growth hormone, insulin [32]. Furthermore, these hormones are contributed to protein synthesis [33-36]. These findings are in agreement with those of previous studies, which found that arginine and its metabolites are responsible for the secretion of insulin and growth hormone and influence piglet growth [18,37,38]. When mice fed with an arginine-free diet are weaned, their citrulline production increases, and the mice achieve normal weight [39]. Furthermore, citrulline administration increases the body weight and average daily gain in suckling piglets, and the suitable adding dose is 0.29 g/kg/day [12]. However, the precise mechanisms behind these processes remain unclear.

Citrulline and muscle performance

Animal muscle performance is related to the supply of certain nutrients. It's reported that citrulline could be transported to rat aortic smooth muscle cells by a low-affinity carrier with characteristics resembling systems L and N [40]. Citrulline exerts its promotion effects on muscle performance by enhancing muscle protein synthesis and protecting the muscle cells from atrophy [14,41-44]. The supply of citrulline increases the synthesis rate of muscle protein by 33% in male rats [45]. Citrulline affects muscle protein synthesis by the following action: increasing myofibrillar protein synthesis [41]; enhancing the expression of skeletal muscle myofibrillar constituents [14]; improving insulin levels [42]; and increasing muscle mass, content, strength, and motor activity[46]. The positive effect of citrulline on muscles is related to three mechanisms. First, the implication of the NO pathway. NO synthesis depends on NOS, which includes nNOS, eNOS, and iNOS [47]. L-citrulline supplementation significantly increases protein synthesis rate and the diameter of C2C12 myotubes incubated in HBS or serum free media and in the presence of NOS inhibitors (NG-nitro-L-arginine methyl ester (L-NAME) and aminoguanidine). L-citrulline significantly increases *iNOS* gene expression [48]. In one study, male Wistar rats were assigned to four groups: recovered, 1-(2-Trifluoromethyl-phenyl)-Imidazole (TRIM), L-NAME, and control. The TRIM is also an inhibitor of NOS. The cross-sectional area of skeletal muscle in the recovered group reached complete muscle regrowth which exceeds the l-NAME and TRIM group after 10 days of immobilization and 7 days of recovery [49]. These results show that the NOS pathway is vital for the regrowth of immobilized muscles. Moreover, the activation of the mTOR pathway is involved in the muscle regulation process. mTOR expression in the recovery group of male Wistar rats was enhanced compared to the control group and the increase was blocked in the l-NAME and TRIM groups after 10 days of immobilization and 7 days of recovery [49]. Moreover, citrulline activates the phosphorylation of mTORC1 pathway downstream molecules, such as S6K1 and 4E-BP1, in *in vitro* cultured myotubes and malnourished aged rats [43,50-52]. These findings suggest that citrulline regulates muscle performance possibly by activating mTOR in muscle protein synthesis. Finally, the hypothalamus is one of the possible anatomical sites in which citrulline may modulate muscle performance. Hypothalamus is the center of the endocrine and nervous systems. The activity and amount of tyrosine hydroxylase is a rate-limiting enzyme to dopamine synthesis from tyrosine [53-55]. In aged rats, citrulline supplementation improves the total tyrosine hydroxylase numbers and locomotor activity [56]. Thus, citrulline can regulate daily activities by the dopaminergic pathway. Furthermore, the arginine group (injected L-arginine) increases the total workload of exercise and nNOS-positive cell numbers in the paraventricular nucleus and dorsomedial hypothalamus, decreases the athletic ability of the L-NAME group (injected L-NAME), and exerts no significant effect on the quantity of nNOS-positive cells in rats [57]. These results show that hypothalamic NO participates in regulating the exercise performance of rats. In conclusion, citrulline supplementation obviously enhances animal muscle performance through the NO pathway, mTOR pathway, and the hypothalamus is one of the sites of action.

Citrulline and Intestinal Homeostasis

Citrulline not only adjusts protein synthesis but also exerts certain effects of regulating intestinal homeostasis. The gut is the main source of plasma citrulline; hence, citrulline concentration is an indicator of enterocyte function and quality [58]. Additionally, citrulline can be effectively transported into the intestine through several pathways such as carrier-mediated active transport system in everted sacs of the small intestine [59], the Na^+-dependent (system $B^{0,+}$) and the Na^+-independent uptake (systems L and $b^{0,+}$) in the Caco-2 cells [60], and a neutral amino acid transport system in the hamster intestine [61]. The intestinal homeostasis of animals is responsible for their normal

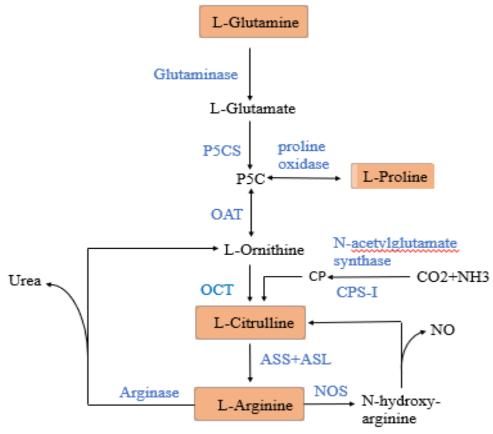

Figure 2: Scheme of synthesis of L-citrulline [2]. P5C: l-Δ1-Pyrroline-5-Carboxylate; P5CS: Pyrroline-5-Carboxylate Synthase; OAT: Ornithine Aminotransferase; OCT: Ornithine Carbamoyltransferase; ASS: Argininosuccinate Synthetase; ASL: Argininosuccinate Lyase; CP: Carbamoyl Phosphate; CPS-I: Carbamoyl-Phosphate Synthase I; NOS: Nitric Oxide Synthase.

growth and development. The normalization of gut barrier function is one of the important aspects of intestinal homeostasis. The gut barrier is the sum of the structures and functions that prevent intestinal harmful substances, such as bacteria and toxins, from passing through the intestinal mucosa and from being circulated in the blood [62]. The intestinal barrier includes physical, chemical, microbial, and immunological barriers, all of which are related to intestinal health [63]. Citrulline exerts its effects on maintaining intestinal homeostasis by protecting the gut barrier function, promoting intestinal digestion and absorption, and inhibiting intestinal cell apoptosis.

Citrulline and gut barrier function

Citrulline and intestinal physical barrier: Epithelial tight junctions are vital for proper maintenance of intestinal barrier function. Citrulline exerts its modulation effects by regulating the intestinal tight junction and integrity of the intestinal mucosa. Dietary supplementation with L-citrulline enhanced ileal tight junctions in the case of ileum coinfected with malaria and nontyphoidal *Salmonella serotypes* which impaired intestinal barrier in a mouse model [64]. Additionally, a female C57BL/6J mice model trial which fed with western-style diet and citrulline showed that mice fed a western-style diet + citrulline diet has a significantly higher level of tight junction proteins occludin and zonula occludens-1 in duodenum [65]. Moreover, the trans epithelial electrical resistance ratio is the index that reflects the permeability of cell membranes. Citrulline improves the mean transepithelial electrical resistance ratio of jejunal IPEC-J2 cell monolayers in neonatal piglets and decreases the inulin flux across the hypoxic monolayers after exposure to hypoxia [8]. Hence, citrulline supplementation contributes to the maintenance of the tight junctions and integrity of intestinal epithelial cells. In a murine mucositis model, citrulline administration attenuates damage to the mucosal architecture, decreasing the size of the injured areas and permeability of the small intestine [9]. Additionally, the protective effects of citrulline in the intestinal epithelial cells are prevented in the presence of irreversible NOS inhibitors [8]. Thus, the efficiency of citrulline in intestinal epithelial cells depends on the NO pathway. Therefore, citrulline can regulate the intestinal physical barrier by affecting intestinal mucosa cell junctions, integrity, and permeability.

Citrulline and intestinal immune barrier: The intestinal tract is the largest peripheral immune organ in animals. The intestinal mucosa associated with lymphoid tissue contains more immune cells than other tissues in the body. The intestinal mucosa immune cells secrete various regulatory substances involved in the immune response, including many cytokines (IL-6, IL-10, TNF-α, IFN-γ) and immunoglobulins. IL-10 is an anti-inflammatory cytokine. TNF-α, IFN-γ, and IL-6 possess proinflammatory cytokine effects [10]. Citrulline can affect the intestinal immune barrier through three channels. First, citrulline affects the levels of proinflammatory or anti-inflammatory cytokines. Oral citrulline significantly decreases the jejunal content of TNF-α and IL-6 in the male rat jejunum model of ischemia–reperfusion injury and resistin (an adipose-derived peptide hormone) levels without impairing the secretion of anti-inflammatory cytokines (IL-10 and adiponectin) [11,66]; this process provides a safe means of immunomodulation that preserves the anti-inflammatory mediator response. Citrulline supplementation reduces IFN-γ levels and maintains IL-10 levels, which may decrease overall mucosa inflammation [67]. Second, citrulline regulates immunoglobulins, including IgA (including sIgA), IgG, and IgM. Citrulline supplementation increases IgA, IgG, and IgM levels and improves the immunity of suckling piglets [12]. SIgA, a secretory immunoglobulin, participates in the generation of local immune response. It neutralizes the antigen, forms the antigen–antibody complexes, and prevents bacterial adhesion to the intestinal mucosa to prevent the bacteria from entering the intestinal wall [68]. Pretreatment with citrulline can significantly stimulate the intestinal production of sIgA and reduce bacterial translocation [17]. Third, immune cells play critical roles in suppressing the immune response. Neutrophil infiltration is one of the manifestations of inflammation. Citrulline supplementation reduces neutrophil infiltration in the intestinal mucosa [69]. Therefore, neutrophils and macrophages are involved in the regulation process of citrulline in the intestinal mucosa. In summary, citrulline can affect the intestinal immune barrier by regulating cytokine, immunoglobulin, and macrophage levels.

Citrulline and intestinal digestion and absorption

The intestinal tract is the largest digestive organ of the body. Animal life activities depend on intestinal digestion and absorption, which provide nutrition to sustain life. The intestinal epithelium can absorb nutrients and water and block various antigens and toxins [70]. Citrulline supplementation increases the villus length of the duodenum in suckling piglets [12]. Moreover, citrulline promotes the piglet's digestion and nutrient absorption ability for growth [12]. Citrulline levels can effectively reflect intestinal digestion and absorption capacity [71]. In patients with short bowel syndrome, post-absorptive plasma citrulline concentration is significantly correlated with the net digestive absorption of protein and fat [72]. It also reflects the mass of absorptive enterocyte and the functional absorptive bowel length [72,73]. Therefore, citrulline exerts positive effects on intestinal digestion and absorption, but the exact molecular mechanisms remain unclear.

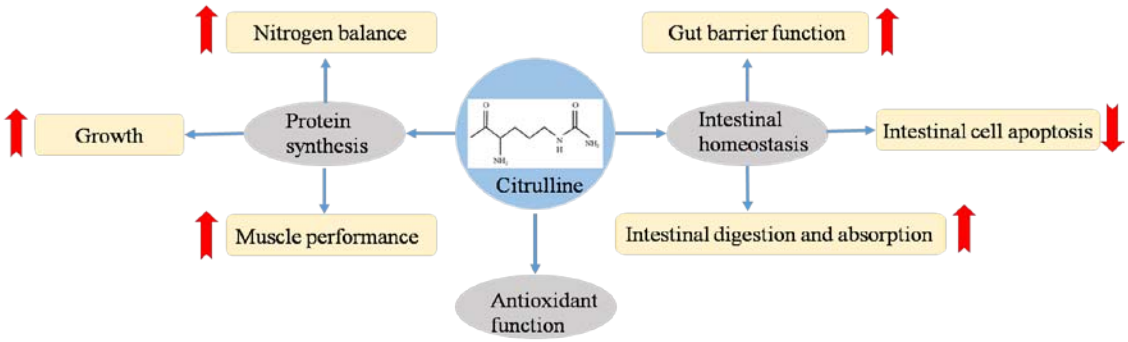

Figure 3: Citrulline: modulation on protein synthesis and intestinal homeostasis.

Citrulline and intestinal cell apoptosis

Intestinal epithelial homeostasis depends on a balance between cell proliferation and apoptosis. Apoptosis, or programmed cell death, is a key factor to control the number of intestinal epithelial cells [74]. Any reason that increases or decreases cell apoptosis may contribute to mucosal atrophy or tumor formation and thus hinder intestinal function [75]. Citrulline has an obvious influence on intestinal cell apoptosis through the NO pathway. NO is synthesized from citrulline, and low NO concentrations protect cells from apoptosis [76]. The antiapoptotic effects of NO are related to the modulation of cyclic nucleotides and ceramide and inhibition of caspases by S-nitrosylation and mitochondrial respiration [13]. In addition, citrulline attenuates jejunal apoptosis through devitalization of the NOS and NF-κB pathways in male Wistar rats [11]. In conclusion, citrulline administration decreases intestinal cell apoptosis.

Citrulline and Antioxidant Function

In normal state, the oxidant and antioxidant abilities of animals are in dynamic equilibrium. Free radicals can make strong reaction with the protein, fat, nucleotides and carbohydrate molecules. When intracellular accumulate lots of free radicals, there will be occurrence of cell apoptosis, cell membrane permeability and barrier function changes and immune damage [77]. Citrulline exhibits certain antioxidant functions. Citrulline can effectively protect plant DNA and enzymes from damage by reactive oxygen species [78]. In animal models, citrulline can effectively reduce the harm caused by oxidative stress. Citrulline supplementation limits lipoprotein oxidation and decreases protein carbonylation and thiobarbituric acid (the final product of lipid peroxidation) reactive substances in elderly rats and in plasma [4,15]. Therefore, citrulline supplementation significantly contributes to antioxidant function.

Conclusion

Citrulline is a highly promising nutrient that has well-defined roles in nitrogen homeostasis and gut homeostasis. In recent years, it has been shown to modulate protein synthesis, intestinal homeostasis and antioxidant capacity (Figure 3). However, the precise mechanism of citrulline in the regulation of intestinal function, e.g., as intestinal barrier, remains unclear. Moreover, the internal molecular mechanism of citrulline for the control of gut digestion and absorption and its antioxidant function are not yet clearly understood. An in-depth study of citrulline to clarify its mechanism of action in maintaining intestinal function will provide new ideas to strengthen animal intestinal health, improve livestock production performance, and promote husbandry development.

Acknowledgment

This project was supported by the Program for Discipline Construction in Sichuan Agricultural University (No. 03570126) for financial support.

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Int J Nutr Sci - Volume 4 Issue 2 - 2019
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Citation: Xu XM, Wu CM, Jia G, Zhao H, Chen XL, Wang J, et al. Citrulline: Modulation on Protein Synthesis, Intestinal Homeostasis and Antioxidant Status. Int J Nutr Sci. 2019; 4(2): 1033.