Is glutamine still an important precursor of citrulline?

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GLUTAMINE AND ARGinine are two amino acids that have received inexhaustible attention by different research groups all over the world over the past decades. This attention is justified by their potential to enhance recovery of surgical and critically ill patients. The beneficial potential of glutamine and arginine is furthermore supported by numerous trials and an ongoing meta-analysis in surgical and critically ill patients who received a supplemental amount of glutamine or arginine (www.criticalcarenutrition.com).

In this issue of this Journal, Tomlinson et al. (28) present the results of a study in healthy humans about the precursor relation between glutamine and arginine. Apart from the clinical importance of glutamine and arginine as addressed above, the relationship between the two amino acids has gained interest due to the assumed importance of glutamine as a nitrogen and carbon donor for the synthesis of arginine. The importance of glutamine as an important precursor for the synthesis of citrulline, the sole precursor for the de novo synthesis of arginine, was previously established in animal studies by Windmueller and Spaeth and others many years ago (31–34) (Fig. 1). In addition, several studies in animals and humans confirmed the important precursor relationship between glutamine, citrulline, and arginine by showing that plasma levels of citrulline and arginine increased after provision of glutamine (6, 8, 11, 12, 22, 23, 25, 26, 35) (Fig. 2). Also, high correlations were observed between intestinal arterial glutamine uptake and venous release of citrulline (8). Debate about the safety of arginine supplementation in septic critically ill patients (9, 10, 27) and the use of high dosages of glutamine in clinical studies that potentially could lead to stimulated arginine synthesis has further contributed to the relevance of investigating the importance of glutamine as a possible precursor for the synthesis of arginine, especially as no harmful side-effects from supplementation of glutamine have been established so far. Therefore, we need to understand this relationship, which will lead to more defined and scientifically based nutritional interventions. This has resulted in a series of stable-isotope studies by us in mice and surgical patients, which established glutamine to be an important precursor for the de novo synthesis of citrulline and arginine (3, 4, 13, 29). However, we believe that more studies are needed when patients are in the fed state and in critically ill patients, administered high dosages of glutamine and arginine (15, 17, 30). If glutamine is proved to be an adequate precursor of arginine, glutamine supplementation will receive further justification in medical practice and in that case could be viewed as having a dual effect. This hypothesis was recently addressed in the review of Vermeulen et al. (30).

However, doubt about the interpretation of the results of mentioned stable-isotope studies and the discussed importance of glutamine as an important precursor for arginine production via the production of citrulline is raised by recent publications of Marini and colleagues (19–21). These authors showed in mice using different isotopomers of glutamine (l-[2-15N], l-[5-15N], and l-[U-13C5]) that glutamine was a poor carbon precursor of citrulline and arginine. Also, glutamine nitrogen was an important source of all nitrogen atoms in citrulline and arginine, indicating a complex role of glutamine as a nitrogen precursor. However, comparison with the previous studies in postabsorptive humans (3, 4, 13, 29) is hampered because the studies by Marini and colleagues were performed in fed mice.

The study in humans by Tomlinson et al. in this issue (28) is the first step of unraveling these important research questions in humans. Their results contradict the findings of Marini and colleagues with respect to the importance of glutamine as a carbon precursor for the synthesis of arginine via the intermediate citruline, because they observed by using the l-[1-15C]glutamine tracer that glutamine contributed 56% to the de novo synthesis of arginine from citruline. This percentage approaches the 64% contribution of glutamine to the de novo synthesis of arginine observed by Ligthart-Melis et al. (13). Also, Tomlinson et al. do not confirm significant labeling of the ureido N by l-[2,15N]glutamine, as observed by Marini et al. (20). Both observations support the notion that results in mice are not easily translated to humans (1, 8). It may be that the metabolic pathways and necessary enzymes are present in the different species but that this does not guarantee that they are quantitatively equally important.

With respect to the applied tracer methodology, Tomlinson et al. (28) seem to use the same precursor-intermediate-product approach as Marini et al. (19–21). This model relies on the intragastric infusion of tracers (precursor) and their recovery as plasma amino acid products of intestinal metabolism. Although Marini and colleagues (19–21) combine this approach with the dilution equation using an additional intravenous tracer to determine whole body rate of appearance of the amino acid product of interest, Tomlinson et al. (28) use the dilution equations straight away. Furthermore, like the mice in studies by Marini and colleagues, the humans in the study by Tomlinson et al. were studied in the fed state. This approach by Tomlinson raises some questions. First, is it justified to use dilution equations when tracers are provided by the gastrointestinal route? The consequence is an overestimation of rate of appearance or
turnover of the amino acid of which the concomitant tracer is provided, because the infusion rate of the tracer is overestimated due to splanchnic extraction of the tracer. Also although less likely, absorption of the tracer could have been reduced because of amino acids coming from the simultaneously ingested meals. With this in mind, one could state that Tomlinson et al. may have underestimated the relative contribution of carbon provided by glutamine for the synthesis of citrulline. Furthermore, by conducting only a protocol involving enterally provided tracers it is not clear how much is contributed by the labeled amino acids that have recycled back to the intestines and could have a different metabolic fate (24). To be able to compare the effect of route of delivery, subjects should have received an additional tracer protocol that could be done on a different day, involving intravenous administration of the same tracers. Second, measurement in the fed state will change the relative contribution of the different metabolic pathways (2), which complicates comparison with results from studies in the fasted state (13, 14, 29). Also, the provided food will further add to the dilution of the tracers. Therefore, it is more than likely that the contribution of glutamine-to-arginine biosynthesis depends on the amount and composition of amino acids provided by the diet.

Conclusions

There is no doubt that providing glutamine increases plasma citrulline, and it is more than likely that this increase is caused by increased intestinal citrulline production (7) and that increased plasma citrulline leads to increased arginine production (5). The study by Tomlinson et al. (28) is an important step toward support of this relationship via glutamine-to-citrulline conversion. However, we need additional information from stable-isotope tracer studies that need to be done in those clinical conditions in which it will help to fine-tune and tailor nutritional support with glutamine, arginine, or citrulline to treat arginine deficiencies or to stimulate nitric oxide production (16, 18). Translational research defines that we use our knowledge and capabilities from research in animals and healthy humans to improve the condition of sick patients.

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DISCLOSURES

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Fig. 1. Pathways by which glutamine and arginine are considered to contribute their carbon skeleton to the synthesis of citrulline and arginine.

Fig. 2. Increase in plasma citrulline after ingestion of 14 g of glutamine in 2 h in healthy controls (26).
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