Glutamine: precursor or nitrogen donor for citrulline synthesis?

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TO THE EDITOR: we would like to comment on the recent publication by Marini et al. (6). The authors present an impressive, meticulous analysis of the metabolic pathways by which glutamine contributes to the synthesis of citrulline. Their study in mice shows that glutamine predominantly donates nitrogen and only a limited amount of carbon to the synthesis of citrulline. Therefore, the authors conclude that glutamine is not a true precursor of citrulline and that t-[2-15N]glutamine is an invalid tracer to study this precursor relationship.

Marini et al. (6) do not discuss the mechanism by which glutamine supplementation is able to enhance plasma levels of citrulline in humans (2, 7–10, 12) if not by providing a substantial part of its carbon skeleton. We think that a possible explanation for their contradictory findings could be the difference between species. To our knowledge, only two stable isotope studies on the metabolic relationship between glutamine and citrulline have been performed in mice (1, 6). The t-[2-15N]glutamine and t-[13C-ureido]-5,5,2H2-citrulline tracers used in mice were also used by us to quantify the turnover of glutamine into citrulline in humans (1, 4, 5, 11). Noteworthy is that the mice studies were performed using large tracer (mass) dosages, whereas we used very small tracer dosages in the human studies. The results of these studies were strikingly different. The studies in mice showed that glutamine contributed only between 15 and 36% to the turnover of citrulline (1), whereas glutamine contributed ~83% to the turnover of citrulline in humans (4). Furthermore, in mice, despite the large amount of administered glutamine, the rate of appearance of citrulline was not enhanced when compared with a control group not receiving glutamine (3). This is in contrast with the response in humans (2, 7–10, 12). Together these observations provide an argument against the legitimacy of direct translation of results in mice to humans.

With respect to the second conclusion, the authors clearly showed that t-[2-15N]glutamine may be a less valid tracer to establish the contribution of the carbon skeleton of glutamine to the synthesis of citrulline when positional information on the label is not provided. Our studies were performed with liquid chromatography-mass spectrometry equipment and analysis techniques that could not differentiate between the possible positions of the isotope in citrulline. Marini et al. (6) did an excellent job by providing this information in their study in mice, although human metabolism may treat the t-[2,15N]glutamine differently. We agree that for future in vivo stable isotope studies it may be necessary to provide positional information on the isotopes present in the infused labeled molecule and its products.

In summary, we would like to state that caution is warranted when results in mice are translated to humans and that knowledge of the position of the label in the conversion products of a stable isotope tracer will be pivotal for future in vivo stable isotope studies.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES