Reply to Ligthart-Melis et al.

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REPLY: we want to thank Ligthart-Mellis et al. (3) for their kind compliments on our recent publication as well as their feedback. We agree with their comments that results obtained in rodents might not be directly translated to humans and that all results obtained with animal models should be evaluated with caution. However, this is not the only difference between our recent publication [Marini et al. (4)] and the articles cited by Ligthart-Melis et al. (1, 2) and Melis et al. (5). The human studies referenced were conducted in patients undergoing gastrointestinal surgery (1, 2) and liver resection due to colorectal cancer (5), whereas our studies were done in conscious mice. How sedation or those disease processes may alter citrulline metabolism is not known, but it is a topic that warrants further investigation.

The limitation of the L-[2-15N]glutamine tracer for the determination of precursor relationship between glutamine and citrulline resides in the biochemical pathway of citrulline synthesis. Although species differences may exist between mice and humans, these will likely be regarding the rate of glutamine utilization and not on the fate of the [2-15N] label. The contribution of glutamine to citrulline synthesis, if any, is done through glutamate. However, glutamate serves as both the precursor for glutamate semialdehyde and as a nitrogen donor for ornithine in a reaction catalyzed by ornithine amino transferase. Therefore, the amino nitrogen of glutamate (and thus the [2-15N] label of glutamine) is the origin of both nitrogen groups of ornithine. Furthermore, the extensive oxidation of glutamine and glutamate by the intestine also generates ammonia, which can be utilized for the synthesis of carbomyl phosphate and thus be incorporated in the ureido group of citrulline. A recent report in healthy humans (6) has shown that in fact the infusion of L-[2-15N]glutamine labels citrulline in its 2 and 5 positions to a similar extent. Our preliminary data in septic patients show identical results.

In summary, the advent of MS/MS technology will be central to further the field of tracer kinetics, allowing researchers to trace the different moieties of the molecules studied, and to determine the contribution of multiple precursors to their synthesis in in vivo systems.

DISCLOSURES

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

REFERENCES