Dietary Protein and the Blood Glucose Concentration

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Body proteins are being synthesized and degraded continuously (1). The estimated turnover is ~210 g/day (2). Amino acids resulting from protein degradation can be recycled (reused for synthesis), but this is incomplete. Therefore, dietary protein is necessary for maintenance of lean body mass. Also, dietary protein is required to replace protein lost from the shedding of skin, hair, nails, cells in the gastrointestinal tract, and protein-containing secretions. However, the actual losses are estimated to be only 6–8 g/day (3).

Overall, approximately ~32–46 g of high-quality dietary protein/day is reported to be required to maintain protein balance (2). This is considerably less than amounts of protein reportedly consumed by American adults (~65–100+ g/day) (4). The excess food-derived amino acids then are oxidized as fuel directly or indirectly after conversion to glucose.

In 1915, using a phlorhizinized dog preparation, Janney (5) demonstrated clearly that the deaminated amino acids (carbon skeletons) present in dietary proteins could be used to produce glucose endogenously. For most common proteins, 50–80 g of glucose can be derived from 100 g of ingested protein. Nevertheless, as early as 1913, Jacobson (6) reported that ingestion of proteins did not raise the blood glucose.

Later, in 1924, MacLean (7) fed 50 g of meat protein to two subjects, one with and one without mild diabetes. The theoretical amount of glucose that could be produced was 25 g. However, there was no change in blood glucose. He then fed the subjects 25 g glucose and the blood glucose was clearly elevated. In 1936, Conn and Newburgh (8) reported that ingestion of even a very large amount of protein as meat (1.3 pounds, 0.59 kg), did not raise the blood glucose.

Subsequently, the degradation pathways for each amino acid were elucidated. Of the 20 amino acids found in proteins, all but leucine could, at least in part, be converted into glucose and thus contribute to the circulating glucose pool. However, data from many laboratories, including our own, confirmed that ingested protein per se does not increase the circulating glucose concentration (9,10). The reason for this remained unknown.

In order to address this issue, a number of years ago (11) we determined the actual amount of glucose entering the circulating glucose pool using a glucose isotope-dilution technique. Urea formation was determined as an index of the amount of ingested protein deaminated, and the carbon skeletons available for glucose synthesis. Normal, young subjects ingested 50 g of cottage cheese protein (casein). It was calculated that 34 g were deaminated (68%) over the 8 h of the study. The amount of glucose produced and entering the circulation was only 9.7 g (11). Thus, the amount of glucose produced was considerably less than the amount theorized (~25 g). The plasma glucose concentration did not change.

Later, in people with untreated type 2 diabetes, ingestion of 50 g beef protein was calculated to result in only 2.0 g of additional glucose added to the circulation over the 8-h study period (12). These results were rather surprising because, as expected, the basal glucose production rate in the diabetic subjects was greater than that in normal young subjects (13–15).

Interestingly, numerous studies now have demonstrated that provision of any of the commonly ingested gluconeogenic substrates, fructose, galactose, glycerol, as well as amino acids, when infused or ingested do not, or only modestly, increase hepatic production and release of glucose (16) and have little effect on the circulating glucose concentration. This is due to a hepatic autoregulatory process which is independent of a change in the circulating insulin or glucagon concentrations (17,18).

In this issue of *Diabetes*, Fromentin et al. (19) have elegantly addressed the issue of the endogenous partitioning of the absorbed amino acids derived from a food (egg) protein. They specifically address the disposition of the carbon skeletons derived from the total amino acids and the appearance rate and quantity of glucose entering the plasma pool over an 8-h period using multitracer technology.

Their study is unique in four ways: First, whole eggs were used as a source of protein, i.e., a modest amount of fat as well as protein was ingested. Second, the amount of protein ingested (23 g) was lower than others had used and is well within an amount likely to be ingested in a single meal. Third, diet-derived carbon and nitrogen stable-isotope tracers were used. Thus, both the fate of the amino moiety as well as the amino acid carbon chains were traced. This labeling was accomplished by adding doubly labeled amino acids to the diet of laying hens. Fourth, subjects were encouraged to ingest a defined diet containing 14% protein for 5 days prior to the study.

The authors calculated that ~18 g (79%) of the 23 g of ingested protein could be accounted for by deamination; thus those carbon skeletons were available for gluconeogenesis and release of new glucose into the circulation. The remainder, presumably, was used for new protein synthesis.

The total amount of glucose entering the circulation from all sources was calculated to be 50 g over the 8-h period. However, only 4 g (8%) could be attributed to the ingested protein. This was less than a theoretical maximum,

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DOI: 10.2337/db12-1829

See accompanying original article, p. 1435.

but as the authors point out, the fractional conversion was the same as we determined previously following casein ingestion (11). This suggests a highly regulated process. The remaining deaminated amino acid carbon appeared as CO_2, i.e., was oxidized as fuel directly.

The data are compelling but need to be interpreted in the context of a lack of a randomized, crossover, 8-h fasting control group. Also the subjects were in negative nitrogen balance (31 g protein oxidized/23 g ingested). Additional studies using larger amounts of protein in subjects either adapted to or not adapted to a high protein diet (~30% of food energy) would be of interest.

Overall, these data clearly indicate that endogenous production and addition of glucose to the circulation from dietary protein are relatively small. The regulatory mechanisms that control the partitioning of the fate of food-derived amino acids between new protein synthesis, deamination, direct oxidation as fuel or conversion into glucose and glucose release into the circulation remain to be determined.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Waterlow JC. Observations on the mechanism of adaptation to low protein intakes. Lancet 1968;2:1091–1097
2. Food and Nutrition Board. Proteins and Amino Acids. In *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC, The National Academies Press, 2005, p. 589–768
3. Carpenter KJ. Protein requirements of adults from an evolutionary perspective. Am J Clin Nutr 1992;55:913–917
4. Fulgoni VL 3rd. Current protein intake in America: analysis of the National Health and Nutrition Examination Survey, 2003-2004. Am J Clin Nutr 2008; 87:1554S–1557S
5. Janney NW. The metabolic relationship of the proteins to glucose. J Biol Chem 1915;20:321–350
6. Jacobsen ATB. Untersuchungen uber den Einfluss verschiedener Nahrungsmittel auf den Blutzucker bei normalen, zuckerkranken und graviden Personen. Biochem Z 1913;56:471–494 [in German]
7. MacLean H. *Modern Methods in the Diagnosis and Treatment of Glycosuria and Diabetes*. London, Constable & Co. Ltd., 1924
8. Conn JW, Newburgh LH. The glycemic response to isoglucogenic quantities of protein and carbohydrate. J Clin Invest 1936;15:665–671
9. Gannon MC, Nuttall FQ. *Protein and Diabetes*. Alexandria, American Diabetes Association, 1999
10. Gannon MC, Nuttall FQ. Amino acid ingestion and glucose metabolism—a review. IUBMB Life 2010;62:660–668
11. Khan MA, Gannon MC, Nuttall FQ. Glucose appearance rate following protein ingestion in normal subjects. J Am Coll Nutr 1992;11:701–706
12. Gannon MC, Nuttall JA, Damberg G, Gupta V, Nuttall FQ. Effect of protein ingestion on the glucose appearance rate in people with type 2 diabetes. J Clin Endocrinol Metab 2001;86:1040–1047
13. Wajngot A, Chandramouli V, Schumann WC, et al. Quantitative contributions of gluconeogenesis to glucose production during fasting in type 2 diabetes mellitus. Metabolism 2001;50:47–52
14. Boden G, Chen X, Stein TP. Gluconeogenesis in moderately and severely hyperglycemic patients with type 2 diabetes mellitus. Am J Physiol Endocrinol Metab 2001;280:E23–E30
15. Basu R, Schwenk WF, Rizza RA. Both fasting glucose production and disappearance are abnormal in people with "mild" and "severe" type 2 diabetes. Am J Physiol Endocrinol Metab 2004;287:E55–E62
16. Nuttall FQ, Ngo A, Gannon MC. Regulation of hepatic glucose production and the role of gluconeogenesis in humans: is the rate of gluconeogenesis constant? Diabetes Metab Res Rev 2008;24:438–458
17. Tappy L, Jéquier E, Schneiter P. Autoregulation of Glucose Production. News Physiol Sci 2000;15:198–202
18. Gerich JE. Control of glycaemia. Baillieres Clin Endocrinol Metab 1993;7: 551–586
19. Fromentin C, Tomé D, Nau F, et al. Dietary proteins contribute little to glucose production, even under optimal gluconeogenic conditions in healthy humans. Diabetes 2013;62:1435–1442