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Abbreviations: SOD, Superoxide dismutase; NO, nitric oxide.

Comment

—to: Krebs M, Brehm A, Krssak M et al. (2003) Direct and indirect effects of amino acids on hepatic glucose metabolism in humans. Diabetologia 46:917–925

To the Editor: The paper by Krebs et al. [1] illustrates a potential difficulty in the interpretation of measurements of gluconeogenesis in man, which applies to the large number of published studies using similar techniques. In these papers, total gluconeogenesis is estimated by subtracting net glycogenolysis (measured by tracking hepatic glycogen content using nuclear magnetic resonance) from endogenous glucose production (EGP) (measured isotopically using [6,6-$^2H_2$]glucose). We have pointed out [2] that this calculation ignores the possible effect of hepatic intralobular functional heterogeneity.

The estimation of EGP depends on the rate of dilution of glucose-specific activity by new unlabelled glucose, the latter principally derived in the fasting state from hepatic periportal gluconeogenesis and hepatic glycogenolysis. As blood passes down the hepatic sinusoid, the specific activity of its glucose content is diluted by unlabelled glucose. During the subsequent passage through the perivenous zone, uptake of glucose [2, 3] reduces the amount of this decreased specific-activity glucose that eventually reaches the assumed single compartment volume of glucose distribution. Thus this compartment receives a lower amount of diminished specific-activity glucose than it would in the absence of perivenous glucose uptake (PVGU), and EGP is underestimated to varying degrees, depending on the conditions. It follows that when the rate of glycogenolysis is subtracted from EGP, the remaining new glucose production is underestimated.

Biological considerations suggest that the interpretation offered by Krebs et al. could be correct in the particular circumstances of their study. But the fact that technology permissible in man does not allow estimation of PVGU should not cause investigators to lose sight of the possibility that results obtained with techniques like those used in [1] could have a very different explanation from those commonly offered. The alternative explanation is that increases in EGP could be due to failure of PVGU, rather than increased gluconeogenesis. An example of this mechanism is seen in adult rats fetally programmed by maternal protein restriction to develop glucose intolerance; their perfused livers overproduce glucose, largely because of failure of perivenous glucose uptake as a result of localised perivenous depletion of glucokinase [2, 3]. In these studies measurements of hepatic glucose uptake, gluconeogenesis and glycogen were made directly, by methods not involving isotopic dilution. The point is of practical importance, as knowledge of the precise biochemical pathology could influence the development of therapeutic strategies in Type 2 diabetes.

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Abbreviations: EGP, endogenous glucose production; PVGU, perivenous glucose uptake.

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