JCI The Journal of Clinical Investigation

Renal contribution to glucose production after a brief fast: fact or fancy?

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J Clin Invest. 1994;93(6):2303-2303. https://doi.org/10.1172/JCI117232.

Editorial

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Although it has been known for years that the kidneys possess the enzymatic capability to synthesize glucose from gluconeogenic precursors it has generally been felt that they do not contribute to whole body glucose production (GP) after an overnight fast. A recent paper by Cersosimo et al. (1) challenges this concept and suggests that the renal contribution to GP may be much more significant than previously thought. We recently reported data (2) that agree with those of Cersosimo et al. (1) (Table I). In both studies (1, 2) catheterization procedures were used to measure net renal balances of labeled and unlabeled glucose. Renal glucose uptake was calculated by dividing the uptake of [^{3}H]glucose by the arterial [^{3}H]glucose specific activity (SA). Renal GP was calculated as the difference between renal glucose uptake and net renal glucose balance. While the kidneys were taking up glucose in a net sense, they were producing glucose at rates equal to 24 (1) and 13% (2) of tracer-determined whole body GP. A similar finding was made in the rat (3). Net renal glucose balance is similar in the dog and human (1, 2, 4), but it remains to be determined whether humans, like dogs, exhibit renal GP after a brief fast.

Indirect support for a renal contribution to tracer-determined GP comes from an earlier study in which hepatic glucose balance was assessed (2). Tracer-determined GP in the overnight fasted dog was ~15 μmol/kg/min while net hepatic glucose output averaged ~11 μmol/kg/min. The hepatic entry rate of glucose (based on hepatic [^{3}H]glucose uptake) averaged ~1.4 μmol/kg/min thus an extra-hepatic source accounted for ~2.6 μmol/kg/min of glucose. Given its magnitude, in all likelihood that source was the kidney.

The question arises, however, as to whether renal GP calculated as described quantitatively represents "real" GP. There are two technical concerns which must be considered. First, the approach assumes that within the kidney the site of uptake of [^{3}H]glucose precedes the site of cold glucose entry. If this is not the case then renal uptake would be underestimated. Since the glucose SA drops only slightly (~5%) across the kidney this assumption is of little consequence. Second, it is unclear whether the reduction in the glucose SA which occurs as blood traverses the kidney is the result of the addition of unlabeled glucose or the loss of labeled glucose in an exchange process. As discussed below this is a more difficult problem.

Renal glucose kinetics are unique in that ~20% of the load of glucose presented to the kidney is filtered at the glomerulus and quantitatively taken into the proximal tubular cells (PTC). Since this cell contains gluconeogenic enzymes (5), has a source of unlabeled glucose-6-phosphate (gluconeogenic precursor uptake), and has a limited but existent glycolytic capacity (5), it is possible that a labeled glucose molecule could exchange with an unlabeled molecule creating "apparent" glucose production. From the perspective of the tracer method it does not matter whether production is "real" or "apparent," and it must be concluded that the kidneys are responsible for a portion, (albeit small 13–24%) of tracer-determined GP even after a brief fast. This implies that tracer-determined GP cannot simply be taken to be liver derived, and data must be interpreted with caution. For example, Rothman et al. (6) recently suggested that gluconeogenesis, in the human was more important after a 22-h fast than previously thought. These authors determined hepatic glycogen loss (i.e., glycogenolysis) using NMR techniques, and GP using [^{3}H]glucose. They then equated gluconeogenesis to the difference between the glycogenolytic rate and whole body GP. If [^{3}H]glucose exchange occurs in the human kidney then their approach overestimates gluconeogenesis. If the renal GP is real then the high gluconeogenic rate they reported could be the result of a combination of hepatic and renal gluconeogenesis.

Table I. Renal and Whole Body Glucose Kinetics (μmol/kg/min) in the Overnight Fasted Conscious Dog

	Net renal glucose uptake	Renal glucose uptake	Renal glucose production	Whole body glucose production
Cersosimo et al. (1) $n = 12$	1.4	5.8	4.4	18.5
McGuiness et al. (2) $n = 14$	1.4	3.3	1.9	15.0

The study of Cersosimo et al. (1) showed a more sensitive response of the kidney to insulin than earlier studies (3, 5). In line with this, McGuinness et al. (2) found that renal GP in the dog also responded to stress hormone infusion. The fact that glucose metabolism by the kidneys changes in response to physiologic alterations in hormone levels makes consideration of the renal contribution even more important.

In summary, it is now clear that in the briefly fasted dog tracer-determined GP reflects both hepatic and renal glucose metabolism. Although the renal contribution is small (13–24%) the kidneys, like the liver, appear to be hormonally responsive. Interpretation of tracer data should include consideration of a renal contribution. Two important issues remain to be resolved. First, does this finding made in the rat and dog apply to man. Second, does the decline in glucose SA which occurs as blood traverses the kidney reflect the "real" addition of cold glucose or an "apparent" addition resulting from the loss of [^{3}H]glucose in an exchange process?

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J. Clin. Invest.
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0021-9738/94/06/2303/01 $2.00
Volume 93, June 1994, 2303