

# Renal Gluconeogenesis

## Its importance in human glucose homeostasis

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Studies conducted over the last 60 years in animals and in vitro have provided considerable evidence that the mammalian kidney can make glucose and release it under various conditions. Until quite recently, however, it was generally believed that the human kidney was not an important source of glucose except during acidosis and after prolonged fasting. This review will summarize early work in animals and humans, discuss methodological problems in assessing renal glucose release in vivo, and present results of recent human studies that provide evidence that the kidney may play a significant role in carbohydrate metabolism under both physiological and pathological conditions.

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To function effectively as a source of fuel in the brain, renal medulla, and nucleated blood cells and to supplement energy provided to other tissues (e.g., muscle and splanchnic organs) by free fatty acids and amino acids, glucose is normally released into the circulation of humans who were fasted overnight (postabsorption) at a rate of 10–11  $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (1). This release of glucose is the result of one of two processes: glycogenolysis and gluconeogenesis. Glycogenolysis involves the breakdown of glycogen to glucose-6-phosphate and its subsequent hydrolysis by glucose-6-phosphatase to free glucose. Gluconeogenesis involves the formation of glucose-6-phosphate from precursors such as lactate, glycerol, and amino acids with its subsequent hydrolysis by glucose-6-phosphatase to free glucose. Liver and skeletal muscle contain most of the body's glycogen stores. However, because only the liver contains glucose-6-phosphatase, the breakdown of hepatic glycogen leads to the release of glucose, whereas the breakdown of muscle glycogen leads to the release of lactate.

This lactate and the lactate generated via glycolysis of glucose from plasma by blood cells, the renal medulla, and other tissues can be absorbed by gluconeogenic organs and re-formed into glucose.

Recent studies using nuclear magnetic resonance (NMR) spectroscopy of changes in hepatic glycogen content (2) indicate that in overnight-fasted normal volunteers, net hepatic glycogenolysis occurred at a rate of  $\sim 5.5 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and accounted for  $45 \pm 6\%$  of the overall release of glucose into the circulation, which was measured isotopically. As indicated earlier, only the liver contains appreciable glycogen and glucose-6-phosphatase, making it the only organ that can directly release glucose as a result of glycogen breakdown. Thus, these data represent total glycogenolysis and indicate that  $\sim 55\%$  of all glucose released into the circulation in the postabsorptive state is a result of gluconeogenesis. It should be pointed out that to a certain extent, this approach may lead to an overestimation of gluconeogenesis' effects resulting from glycogen cycling and other considerations (3).

Various isotopic methods have been used to assess the proportion of overall glucose release attributable to gluconeogenesis in humans. The ingenious approach developed by Landau et al. (4), which uses the ratio of enrichments of the C-2 carbon to the C-5 carbon of plasma glucose after ingestion of deuterated water, appears to be the most widely accepted. Investigators using this approach have found that gluconeogenesis accounted for  $54 \pm 2\%$  of all glucose released into the circulation of overnight-fasted normal volunteers (5). These results are in excellent agreement with those predicted both from NMR studies of hepatic glycogen depletion (2) and from a stable isotope approach using indirect calorimetry ( $51 \pm 5\%$ ) (6), but they are higher than those reported using mass isotopomer distribution analysis during infusions of  $[2-^{13}\text{C}]$ glycerol ( $\sim 36\%$ ) (3).

Only two organs in the human body—the liver and the kidney—possess sufficient gluconeogenic enzyme activity and glucose-6-phosphatase activity to enable them to release glucose into the circulation as a result of gluconeogenesis. As we will later discuss, a wealth of animal experiments performed over the last 60 years have provided evidence that both the liver and the kidney release glucose into the circulation under a variety of conditions (7). Nevertheless, until quite recently, it was thought that the liver was the sole site of gluconeogenesis in normal postabsorptive individuals and that the kidney became an important source of glucose only in acidotic conditions or after prolonged fasting (8). In fact, the literature is replete with publications that refer to isotopic measurements of the overall release of glucose into the circulation as hepatic glucose output.

However, the concept that the liver is the sole source of glucose, except in acidotic conditions and after prolonged fasting, has been challenged on several grounds. First, the classic studies of Felig et al. (9), Wahren et al. (10), and Ahlborg et al. (11) indicated that net splanchnic uptake of gluconeogenic precursors could maximally account for only 20–25% of glucose release (not 36–55%), assuming that 100% of the net uptake of these precursors were incorporated into glucose by the liver. Indeed, these

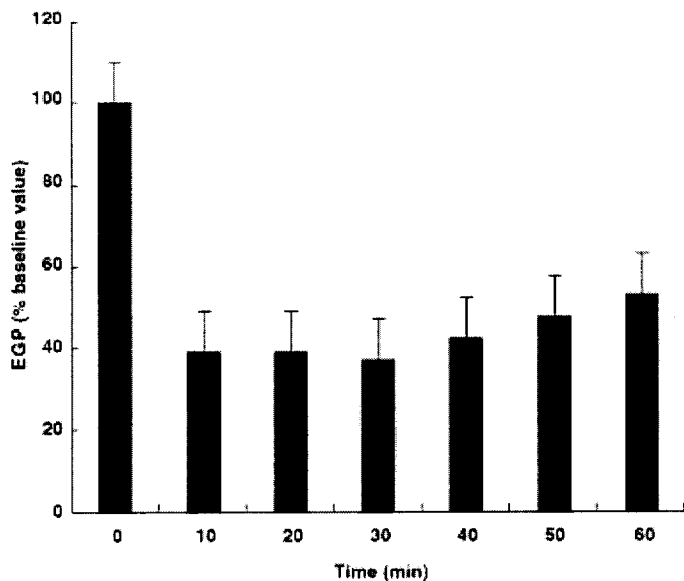
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**Abbreviations:** NMR, nuclear magnetic resonance.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.



**Figure 1**—Endogenous glucose release (EGP) before and after removal of the liver in individuals undergoing liver transplantation. Reproduced from Joseph et al. (13) with permission.

values might be overestimations, because portal venous lactate, glycerol, and amino acid levels are generally equal to or lower than arterial levels (12). Second, in individuals undergoing liver transplantation, endogenous glucose release does not drop to zero after removal of the liver (13,14); indeed, Joseph et al. (13) (Fig. 1) reported that 1 h after removal of the liver, endogenous glucose release decreases by only ~50%. Finally, recent studies using a combination of net renal glucose balance and isotopic measurements have demonstrated that the kidney releases significant amounts of glucose in postabsorptive normal volunteers (7). This article resummaries and updates current information on human renal glucose metabolism as recently reviewed by Meyer and Gerich (7).

### EARLY NONHUMAN STUDIES

In 1938, Bergman and Drury (15) presented the first evidence that the kidney might release glucose and be important for maintenance of normal glucose homeostasis. These investigators used the glucose clamp technique to maintain euglycemia in two groups of rabbits—one functionally hepatectomized and one functionally hepatectomized and nephrectomized. As shown in Fig. 2, functional removal of the kidneys in hepatectomized animals led to an abrupt increase in the amount of glucose required to maintain euglycemia, results that would be consistent with the hypothesis that the kidneys are a source of plasma glucose.

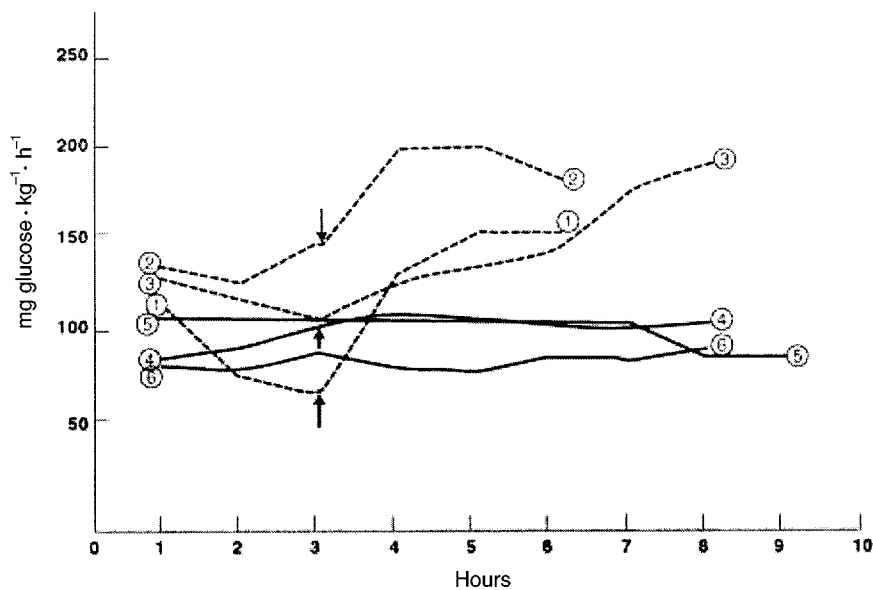
Shortly thereafter, Reinecke (16) reproduced such results in rats, but also measured arteriovenous glucose concentrations in the hepatectomized animals. It was found that renal vein glucose levels exceeded arterial levels as the animals became hypoglycemic, thus demonstrating that under these conditions, the kidneys released glucose into the circulation.

Several years later, Drury et al. (17) corroborated this conclusion using isotopic

methods. These investigators injected  $^{14}\text{C}$ -labeled glucose into groups of rats that had been either hepatectomized or hepatectomized and nephrectomized. In the former group, there was dilution of the plasma glucose  $^{14}\text{C}$  specific activity as the animals became hypoglycemic, indicating the release of unlabeled (i.e., endogenously produced) glucose into the circulation from some source other than the liver. Dilution of the plasma specific activity of the injected glucose did not occur in hepatectomized animals that had been nephrectomized, providing evidence that the source of the endogenous glucose released into the circulation after hepatectomy was the kidney.

Four years later, Teng (18) reported that renal cortical slices taken from animals with experimentally induced diabetes released glucose at an increased rate, but that treatment of the animals with insulin could reverse this effect. In 1960, using a similar model, Landau (19) demonstrated that gluconeogenesis from pyruvate was increased more than twofold by the diabetic kidney.

Near that time, Krebs began a series of experiments characterizing the substrates used for renal gluconeogenesis (20), the capacity of the kidney for gluconeogenesis in different species (21), and various aspects of the regulation of renal gluconeogenesis (22,23), including its stimulation by free fatty acids (24). Because the kidney had a greater concentration of gluconeogenic enzymes (in terms of weight)



**Figure 2**—Effect of functional nephrectomy on glucose requirements to maintain euglycemia in hepatectomized rabbits. ---, Functionally nephrectomized-hepatectomized animals; —, functionally hepatectomized animals. Reproduced from Bergman and Drury (15) with permission.

Table 1—Early human net renal glucose balance studies

Reference	Study group	Finding
Meriel et al., 1958 (82)	15 postabsorptive patients with various disorders	No AV difference
Aber et al., 1966 (26)	10 postabsorptive patients with pulmonary disease	NRGR, correlated with acidosis
Nieth and Schollmeyer, 1966 (44)	58 postabsorptive patients with renal disease	No AV difference
Owen et al., 1969 (27)	5 obese individuals fasted 35–41 days	NRGR 44% of NSGO
Björkman et al., 1980 (28)	17 60-h fasted normal volunteers	NRGR 14% of NSGO
Björkman and Felig, 1982 (83)	6 60-h fasted normal volunteers	No AV difference
Björkman et al., 1989 (84)	5 postabsorptive normal volunteers	No AV difference
Ahlborg et al., 1992 (49)	6 postabsorptive normal volunteers	No AV difference
Brundin and Wahren, 1994 (50)	8 postabsorptive normal volunteers	No AV difference

AV, arteriovenous; NRGR, net renal glucose release; NSGO, net splanchnic glucose release.

than the liver, and because both organs had comparable blood flows (and hence comparable provision of gluconeogenic precursors), Krebs hypothesized that the kidney might be as important a gluconeogenic organ *in vivo* as the liver (23,25).

Given these data, one may ask why the kidney was not considered an important source of glucose in humans. Failure to recognize the limitations of net balance experiments and analytical problems are probably the major reasons.

### EARLY HUMAN STUDIES

— Studies of human renal glucose metabolism began in the late 1950s and focused on measurements of differences between arterial and renal venous glucose concentrations. Such experiments yielded information concerning the net glucose balance across the kidney, *i.e.*, the difference between the production and the utilization of glucose by the kidney. As summarized in Table 1, most investigators found little or no arteriovenous differences in glucose concentrations in nondiabetic overnight-fasted humans, indicating little or no net glucose release by the kidneys. By not taking into consideration the fact that the kidney simultaneously produces and consumes glucose (see below), it was erroneously concluded that the kidney did not release glucose in postabsorptive humans.

In 1966, Aber et al. (26) found that there was net renal glucose release in patients with pulmonary disease, which was negatively correlated with arterial pH (*i.e.*, the greater the acidosis, the greater the net renal glucose release). Shortly thereafter, Owen et al. (27) demonstrated that there was substantial net renal glucose release in morbidly obese patients who fasted for 5–6 weeks. From these observations, there evolved the current textbook

view that the liver was the sole source of glucose, except after prolonged fasting or under acidotic conditions. It is worth noting, however, that Aber et al. (26) did find net renal glucose release in nonacidotic pulmonary patients and that Björkman et al. (28) found significant net renal glucose release in normal volunteers who fasted for only 60 h. Nevertheless, we must emphasize that net balance measurements underestimate renal glucose release to the extent that the kidney takes up glucose.

### PHYSIOLOGICAL CONSIDERATIONS

— The kidney can be considered two separate organs because glucose utilization occurs predominantly in the renal medulla, whereas glucose release is confined to the renal cortex (29–31). This functional partition is a result of differences in the distribution of various enzymes along the nephron. For example, cells in the renal medulla have appreciable glucose-phosphorylating and glycolytic enzyme activity, and, like the brain, they are obligate users of glucose (32). These cells, however, lack glucose-6-phosphatase and other gluconeogenic enzymes. Thus, although they can take up, phosphorylate, glycolyze, and accumulate glycogen, they cannot release free glucose into the circulation (29–31). On the other hand, cells in the renal cortex possess gluconeogenic enzymes (including glucose-6-phosphatase), and thus they can make and release glucose into the circulation. But these cells have little phosphorylating capacity and, under normal conditions, they cannot synthesize appreciable concentrations of glycogen (29–31). Therefore, the release of glucose by the normal kidney is mainly, if not exclusively, a result of renal cortical gluconeogenesis, whereas glucose uptake and utilization occur in other parts of the kidney.

Because the kidney is both a consumer and producer of glucose, net balance measurements do not provide information on the individual processes of renal glucose production and utilization. For example, let us assume that the net balance of glucose across the kidney is zero (*i.e.*, arterial and renal venous glucose concentrations are equivalent), as has been commonly observed in postabsorptive humans. Let us further assume that the kidney uses glucose at a rate of 100  $\mu\text{mol}/\text{min}$ , as has been reported in postabsorptive humans (33). For the law of conservation of matter to hold, the kidney must also release glucose at a rate of 100  $\mu\text{mol}/\text{min}$ . Thus, under these circumstances, the net balance approach will underestimate renal glucose release. To measure renal glucose release *in vivo*, it is necessary to use a combined isotopic-net balance approach, which permits simultaneous determination of renal glucose utilization and renal glucose release (see below).

One might argue that if the net renal glucose release is negligible, the kidneys are not important, because their removal or absence would lead to comparable decrements in glucose release and uptake, causing no net overall change in glucose homeostasis. This, of course, is a theoretical construct that ignores the numerous metabolic changes that occur in the anephric state. It also ignores the fact that renal glucose release and renal glucose uptake are differentially regulated. But more importantly, it ignores the fact that the calculation of glucose release into the circulation by isotopic techniques depends on the dilution of the infused isotope's specific activity (or enrichment) by the release of unlabeled glucose from the liver and kidney, irrespective of these organs' uptake of glucose. Finally, it ignores the consequences in situations other than the overnight postabsorptive state.

During such situations (e.g., while fasting and after meal ingestion), differential changes in renal glucose release and uptake might be important (see below). For example, after a 60-h fast (34) or during hypoglycemia (35), renal glucose uptake decreases while renal glucose release increases. Therefore, to say that the kidney is negligible because the net renal glucose balance is negligible in the postabsorptive state is to clearly underestimate the potential importance of the kidney.

### METHODOLOGICAL CONSIDERATIONS

— With the combined isotopic–net balance approach, renal glucose release (RGR) is calculated as the difference between the net renal glucose balance (NRGB) and renal glucose uptake (RGU), because NRGB represents the algebraic sum of RGU and RGR:

$$\text{RGR} = \text{NRGB} + \text{RGU}$$

Thus, from the example given above,  $100 \mu\text{mol}/\text{min} = 0 + 100 \mu\text{mol}/\text{min}$ .

NRGB is calculated as the product of the difference between arterial glucose ( $A_G$ ) and renal vein glucose ( $V_G$ ) concentrations and renal blood flow (RBF), as measured by the clearance of paraminohippuric acid (36):

$$\text{NRGB} = (A_G - V_G) \times \text{RBF}$$

RGU is calculated as the product of the fractional extraction of glucose by the kidney (FX), the  $A_G$ , and RBF:

$$\text{RGU} = A_G \times \text{FX} \times \text{RBF}$$

The fractional extraction of glucose by the kidney is calculated from isotopic glucose data as the difference between the amount of tracer entering the kidney and the amount of tracer leaving the kidney divided by the amount of tracer entering the kidney. In practice, the amount of tracer entering and leaving the kidney is usually calculated as the product of the plasma glucose concentrations and the respective specific activities or enrichments, depending on whether stable or radioactive glucose isotopes are used. The following equation considers the case of using radioactive glucose tracers, where GSA stands for glucose specific activity:

$$\text{FX} = \frac{(A_{\text{GSA}} \times A_G - V_{\text{GSA}} \times V_G)}{A_{\text{GSA}} \times A_G}$$

Because only the kidney and liver release glucose into the circulation, use of this combined isotopic–net balance approach permits estimation of hepatic glucose release as the difference between overall glucose release (determined with the same infused isotope used to measure renal glucose fractional extraction) and renal glucose release: hepatic glucose release = overall glucose release – renal glucose release.

Hepatic glucose release can be estimated from measurements of splanchnic glucose fractional extraction and net balance made during catheterization of a hepatic vein (37,38). This approach can also be used to calculate renal glucose release; one would first determine the hepatic (splanchnic) glucose release and then subtract this from the total endogenous glucose release to obtain the renal glucose release. This approach, as well as the net renal balance–isotopic approach, has recently been used by Ekberg et al. (34).

Because renal blood flow is 1,000–1,500 ml/min, arterial–renal venous differences in glucose and tracer concentrations are relatively small. Consequently, analytical imprecision in measuring these parameters can lead to substantial error in calculating renal glucose fluxes, including physiologically impossible negative values for renal glucose fractional extraction, uptake, and release (34,35). It should be noted that although hepatic blood flow is comparable with that of the kidney, larger arterial–hepatic venous differences result in a greater signal-to-noise ratio and generally, but not always (34), obviate this problem. Nevertheless, because the same measurements and equations are used to calculate splanchnic and renal glucose fractional extraction, uptake, and release, comparable analytical imprecision would be expected for determinations of hepatic and renal glucose release. Thus, the coefficients of variation for both hepatic and renal glucose release have been estimated to be ~9% (38).

The major assumption with renal studies is that data obtained from one kidney represent half of the total renal glucose release. This seems reasonable, although catheter displacement can result in both dilution of glucose concentrations and increases in glucose specific activities or enrichments, resulting in underestimations of renal glucose release. On the other hand, with hepatic studies, one must assume that data from one hepatic vein are representative of the whole liver and that portal vein

glucose levels approximate arterial values. The latter is certainly not true after meal ingestion and is probably not true in people with diabetes. Furthermore, the coefficient of variation of measurements in different hepatic veins is ~15%, indicating that results from the catheterization of one hepatic vein may not be representative of the whole liver (39); thus, there may be greater variability with this approach than with the renal vein approach.

When faced with physiologically impossible negative fractional extractions of glucose across the kidney, some investigators have chosen to consider them as zero; other investigators have accepted these data at face value, whereas some have repeated such measurements as well as those considered to yield unrealistically high fractional extractions. The first approach seems reasonable, but it would introduce some bias favoring increased renal glucose uptake, which, by use of the equations described earlier, would lead to the calculation of increased renal glucose release. The second approach is very conservative, but it would have the greatest variance, thus decreasing its power to detect a significant difference in renal glucose release if one were present.

In our studies, we chose the third approach: to rerun specific activity or eliminate an obvious statistical outlier among the triplicates of blood glucose concentrations if either a negative or an exceedingly high fractional extraction was observed. We realize that our approach is not founded on any statistical precedent and could lead to biased or even erroneous results. However, we believe that our use of this approach has not led to such results. For example, in one of our recent experiments (35), 18 of ~200 samples initially yielded negative fractional extractions, and 13 yielded unrealistically high fractional extractions. With our approach (i.e., reassaying samples or deleting obvious statistical outliers), all high fractional extractions were lowered. We found that 15 of the negative fractional extractions became less negative, whereas 3 became more negative. There were still seven negative fractional extractions (3.5% of all determinations). The initial average fractional extraction of all these samples changed from 1.4 to 1.8%. However, because of the robustness of the equations used to calculate renal glucose release (i.e., changes in glucose concentration produce changes in net balance, which affect changes in fractional extraction), renal glu-

**Table 2—Proportion of total glucose release due to renal glucose release in normal postabsorptive humans using the combined isotopic net balance technique**

Reference	Proportion
Moller et al., 1999 (85)	21
Ekberg et al., 1999 (34)	5
Cersosimo et al., 1999 (64)	22
Cersosimo et al., 1999 (53)	25
Meyer et al., 1998 (77)	17
Meyer et al., 1998 (56)	21
Stumvoll et al., 1998 (52)	22
Stumvoll et al., 1998 (57)	22
Meyer et al., 1997 (86)	13
Stumvoll et al., 1995 (58)	28
Mean $\pm$ SEM	20 $\pm$ 2

Data are % of total glucose release.

cose release did not change (1.74 vs. 1.71  $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). Nevertheless, in retrospect it would have been preferable to determine glucose specific activity and concentration measurements with sufficient replicates, allowing us to apply a statistically recognized approach, such as that proposed by Winer (40), to minimize the effects of analytical imprecision.

### RENAL GLUCOSE RELEASE IN POSTABSORPTIVE HUMANS

Given the analytical difficulties in measuring renal and hepatic glucose release in humans, it is not surprising that widely varying results have been reported and that the exact contribution of the kidney to overall glucose release is controversial. Table 2 summarizes the results of all 10 studies, which to date have used the combined isotopic-net renal balance approach to determine renal glucose release in humans. Values between 5 and 28% were found for the contribution of renal glucose release to overall glucose release. The unweighted average (mean  $\pm$  SEM) of all of these studies is 20  $\pm$  2%, with 95% CIs from 8 to 32%.

Although renal glucose release may have been overestimated in studies using zero in place of negative renal glucose fractional extraction values, these data taken as a whole clearly indicate that the human kidney releases glucose into the circulation of normal postabsorptive humans. Consequently, regardless of the absolute contribution of the kidney, it is no longer appropriate to equate whole-body isotopically determined glucose release with

hepatic glucose release, as has been done in the past (41,42). Isotopic determinations of endogenous glucose release should be referred to as endogenous glucose release and not hepatic glucose release.

### RENAL GLUCONEOGENESIS

If one assumes that the average mentioned above (i.e.,  $\sim 20 \pm 2\%$ ) approximates the renal contribution to total glucose release, one can draw inferences regarding the relative importance of the liver and kidney as gluconeogenic organs. Current evidence indicates that in overnight-fasted normal humans, gluconeogenesis accounts for about half of all glucose released into the circulation (2,5). Because all of the glucose released by the kidney can reasonably be ascribed to gluconeogenesis, it would appear that, if renal glucose release accounts for 20% of overall endogenous glucose release, it should be responsible for  $\sim 40\%$  of all gluconeogenesis.

The studies of Felig et al. (9), Wahren et al. (10), and Ahlborg et al. (11) indicated that net splanchnic uptake of gluconeogenic precursors would maximally allow gluconeogenesis by the liver to account for only 20–25% of net splanchnic glucose release. Adding the kidney's contribution to overall gluconeogenesis (based on the combined isotopic-net renal glucose balance approach [ $\sim 20\%$ ]) to that of the liver (based on the net splanchnic uptake of gluconeogenic precursors [20–25%]) could, within experimental error, account for total gluconeogenesis, as assessed by methods yielding the highest values for gluconeogenesis (2–5).

Table 3 shows the results of our studies regarding the net renal uptake of gluconeogenic precursors and their potential contribution to both renal and overall glucose release in postabsorptive normal

volunteers. The net amount of lactate, glutamine, glycerol, and alanine taken up by the kidney could, if wholly converted to glucose, account for  $\sim 20\%$  of all glucose released into the circulation and nearly 90% of the glucose released by the kidney. Because these calculations do not include the net uptake of amino acids other than glutamine and alanine, they may somewhat underestimate the gluconeogenic potential of the kidney. Nevertheless, if gluconeogenesis represents 50% of overall glucose release in the postabsorptive state, these data indicate that renal gluconeogenesis could account for  $\sim 40\%$  of overall gluconeogenesis under these conditions, and they are consistent with independent determinations of the contribution of the kidney to overall gluconeogenesis based on the combined isotopic-net glucose balance experiments of renal glucose release.

Furthermore, these data are also consistent with recent studies by Cersosimo et al. (38), who found that renal net uptake of lactate, alanine, and glycerol could account for 85% of renal glucose release and 21% of overall glucose release. Thus, given the imprecision of the measurements involved in the determination of both gluconeogenesis and the release of glucose by the liver and kidney, for practical purposes, one could consider the kidney as important a gluconeogenic organ as the liver in normal postabsorptive humans.

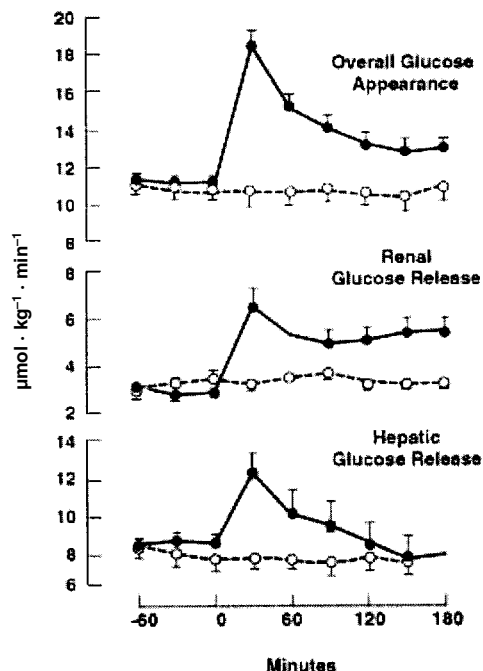
### RENAL GLUCONEOGENIC SUBSTRATES

Lactate, glutamine, alanine, and glycerol are the main gluconeogenic precursors in humans, together accounting for  $>90\%$  of overall gluconeogenesis (1). Although considerable human data are available for renal net balances of gluconeogenic precursors (27,28,43–50),

**Table 3—Relation of net renal uptake of gluconeogenic precursors to overall glucose release and renal glucose release in postabsorptive normal volunteers**

	n	Means $\pm$ SEM
Net renal gluconeogenic precursor uptake ( $\mu\text{mol}/\text{min}$ , glucose equivalents)	58	
Lactate	16	96 $\pm$ 11
Glutamine	37	22 $\pm$ 2
Glycerol	10	30 $\pm$ 5
Alanine	9	7 $\pm$ 5
Overall glucose release* ( $\mu\text{mol}/\text{min}$ )	58	825 $\pm$ 15
Renal glucose release† ( $\mu\text{mol}/\text{min}$ )	58	176 $\pm$ 9

Data are from references 35, 51, 52, 56, and 58 and other unpublished studies. \*Proportion accounted for by renal precursor uptake is 19% (assuming all precursors taken up were converted to glucose). †Proportion accounted for by renal precursor uptake is 88% (assuming all precursors taken up were converted to glucose).



**Figure 3**—Effect of epinephrine infusion on overall, renal, and hepatic glucose release in normal volunteers. ○, Epinephrine (n = 6); ●, saline (n = 4). Reproduced from Stumvoll et al. (58) with permission.

their actual incorporation into glucose by the human kidney has been quantitated in only a few studies (51–53). The largest study, which comprised 48 subjects, indicated that lactate was the most important renal gluconeogenic substrate, followed by glutamine and glycerol (51). Renal conversion to glucose of these precursors accounted for ~50, 70, and 35%, respectively, of their overall systemic gluconeogenesis. In another study, renal glycerol gluconeogenesis accounted for ~17% of its overall conversion to glucose (53). It appears that glutamine is a preferential gluconeogenic substrate for the kidney, whereas alanine is preferentially used by the liver (52).

### HORMONAL CONTROL OF RENAL GLUCOSE RELEASE

Animal and in vitro experiments indicate that insulin, growth hormone, cortisol, and catecholamines influence renal glucose release (29,30). Recently, using the combined isotopic and net balance approach, Cersosimo et al. (54) showed that in dogs, insulin suppressed renal glucose release while stimulating renal glucose uptake. McGuinness et al. (55) demonstrated that an infusion with cortisol, glucagon, and epinephrine increased renal glucose release in dogs. Earlier, Teng (18) and Landau

(19) had reported that renal cortical slices from cortisol-treated rats had increased both renal glucose release and gluconeogenesis. Data in humans are limited to the effects of insulin (53,56), glucagon (57), and epinephrine (58).

In normal postabsorptive humans, two independent groups have demonstrated in euglycemic clamp experiments that physiological increases in insulin concentrations suppress renal glucose release and increase renal glucose uptake (53,56). The suppression of renal glucose release was comparable with that of hepatic glucose release (calculated as the difference between total glucose release and renal glucose release), whereas renal glucose uptake accounted for only a small proportion of total glucose uptake. Cersosimo et al. (38) recently reported that the infusion of insulin reduced the renal net uptake of glycerol but not that of alanine and lactate. Similarly, Meyer et al. (56) found that the infusion of insulin reduced net renal glycerol uptake, increased net lactate uptake, and did not affect alanine net uptake and glutamine uptake. These observations suggest that insulin suppresses renal gluconeogenesis primarily by intrarenal mechanisms rather than by simply reducing substrate delivery. The process could involve shunting precursors away from the gluconeogenic pathway and into the oxidative pathway,

thus compensating for the decreased availability of free fatty acids as an oxidative fuel during the infusion of insulin.

Because insulin reduces renal free fatty acid uptake (56), and since free fatty acids have been shown to stimulate renal gluconeogenesis in vitro (24), insulin suppression of renal glucose release might be partially indirect. Indeed, this would be consistent with observations that the extrahepatic indirect effects of insulin on suppressing endogenous glucose release are mediated by changes in free fatty acids (59,60).

The infusion of glucagon, which increases circulating glucagon levels to those seen during hypoglycemia, has been reported to have no effect on renal glucose release or uptake (57). On the other hand, the infusion of epinephrine, which produces plasma levels similar to those seen during hypoglycemia, was found to increase renal glucose release in a sustained fashion, so that after 2 h, virtually all of the increase in systemic glucose release could be accounted for by renal glucose release (58) (Fig. 3). These results suggest that catecholamines may have more of an effect on renal gluconeogenesis than they do on hepatic gluconeogenesis. Such an action would be consistent with the rich autonomic innervation of the kidney.

In the studies by Stumvoll et al. (58), epinephrine augmented renal glutamine gluconeogenesis more than twofold. Because renal glutamine fractional extraction and uptake were increased by only 50%, it appears that epinephrine augmented renal glutamine gluconeogenesis and perhaps gluconeogenesis from other precursors by not merely increasing substrate availability. Again, the mechanism might involve free fatty acids resulting from the stimulation of lipolysis by epinephrine. This finding is relevant in view of the study by Fanelli et al. (61) showing that adrenergic stimulation of gluconeogenesis during counterregulation of hypoglycemia is largely mediated through free fatty acids.

### PHYSIOLOGICAL/PATHOPHYSIOLOGICAL IMPLICATIONS

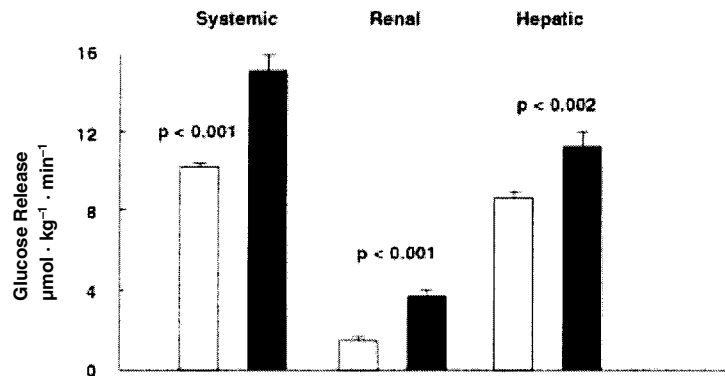
Based on available evidence, it would appear likely that the release of glucose by the kidney may play a significant role in the regulation of glucose homeostasis. Animal and human experiments have provided substantial evidence that the kidney may compensate for impaired hepatic glucose release in maintaining normoglycemia (13–17). Indeed,

two recent human studies have shown that during hepatic transplantation, when patients are without a liver, the kidney can increase its release of glucose to the extent that it can compensate between 50 and 100% of the glucose normally provided by the liver (13,14) (Fig. 1). This may explain why it is extremely uncommon for patients with extensive hepatic malfunction to develop hypoglycemia in the absence of increases in glucose utilization (e.g., during sepsis or heart failure) (62).

**FASTING** — As fasting progresses, liver glycogen stores are depleted and gluconeogenesis becomes the most important process for sustaining the supply of glucose to the brain and other obligate glucose consumers. Several studies (27,28,34) have shown that the kidney increases its net contribution to overall glucose release under these circumstances. In the studies by Ekberg et al. (34), who used the combined isotopic–net balance approach, renal glucose release increased 2.5-fold in 60-h fasted subjects compared with overnight (12-h)–fasted subjects, whereas hepatic glucose release decreased by ~25%. Therefore, one might wonder whether the liver can compensate for the kidney to preserve normoglycemia in patients with renal insufficiency during prolonged fasting.

### HYPOGLYCEMIA

**COUNTERREGULATION** — Counterregulation of hypoglycemia involves both an increased release of glucose into the circulation and decreased tissue glucose uptake (63). In humans, the early increase in glucose release is mainly caused by hepatic glycogenolysis, whereas later it is mainly a result of gluconeogenesis (63). Animal studies cited earlier (16,17) have demonstrated increased renal glucose release during hypoglycemia. Recently, two human studies with similar experimental designs using the hyperinsulinemic-hypoglycemic clamp technique have yielded evidence for an important role of the kidney (35,64). Cersosimo et al. (64) reported that during hypoglycemia (3.6 mmol/l) renal glucose release doubled and its contribution to overall systemic glucose release increased from 22 to 36%. Comparable results were reported by Meyer et al. (35), who found that renal glucose release increased threefold during hypoglycemia (3.2 mmol/l) compared with hyperinsulinemic-euglycemic control experiments. Hepatic glucose release (calculated as the difference between total glucose



**Figure 4**—Renal and hepatic glucose release in type 2 diabetes. □, Nondiabetic; ■, diabetic. Reproduced from Meyer et al. (77) with permission.

release and renal glucose release) increased only 1.4-fold above rates observed during the control experiments, but absolute increments for hepatic and renal glucose release were comparable. Renal glucose uptake during hypoglycemia was reduced 65%, but it accounted for only 5% of the overall reduction in tissue glucose uptake.

These studies provide evidence that the kidney may play an important role in human glucose counterregulation. Conceivably, this role of the kidney could explain why patients with renal failure have a propensity to develop hypoglycemia (65). Furthermore, patients with type 1 diabetes lose their glucagon response to hypoglycemia and become dependent on catecholamine responses (63). One might therefore anticipate that the kidney may play a relatively more important role in glucose counterregulation in such individuals, because lack of a glucagon response would preferentially diminish hepatic glucose release.

### RENAL GLUCOSE METABOLISM IN THE POSTPRANDIAL STATE

— Previous discussions of the role of the kidney in glucose homeostasis have involved the fasting state and hypoglycemia. Another potentially important area is postprandial glucose metabolism. After meal ingestion, endogenous glucose production decreases, and the ingested carbohydrate load is taken up by various tissues, mainly the liver and muscles (42,66). The role of the kidney in postprandial glucose metabolism has recently been investigated (67). Seemingly, renal glucose release paradoxically increases postprandially and it accounts for >50% of the endogenous glucose release for several hours. These obser-

vations suggest that increased renal glucose release may play a role in facilitating efficient liver glycogen repletion by permitting the substantial suppression of hepatic glucose release. The mechanism responsible for this increase in renal glucose release remains to be determined, but it could involve postprandial increases in sympathetic nervous system activity (68) and increases in the availability of gluconeogenic precursors (e.g., lactate and amino acids). Renal glucose uptake apparently does not play a major role in postprandial glucose uptake, because it accounted for <10% of the disposition of the ingested glucose load (67).

### ROLE OF THE KIDNEY IN TYPES 1 AND 2 DIABETES

— It is well established that in type 1 and type 2 diabetes the excessive release of glucose into the circulation is a major factor responsible for fasting hyperglycemia. Increased renal gluconeogenic enzyme activity (69–71) and increased renal glucose release have been consistently demonstrated in studies of diabetic animals (72–75). Indeed, Mithieux et al. (71) demonstrated that there were comparable increases in hepatic and renal glucose-6-phosphatase activity in streptozotocin-induced diabetic rats.

To date, there have been only two studies in human diabetic subjects (one in type 1 diabetes and one in type 2 diabetes) (Fig. 4) that have evaluated renal glucose metabolism with the combined isotopic–net renal glucose balance approach (76,77). Both studies showed that renal glucose release was increased by about the same extent as hepatic glucose release (calculated as the difference between overall glucose release and renal glucose release). A previous study by DeFronzo et al. (78) had

used a combined isotopic–net splanchnic balance approach to measure hepatic glucose release in type 2 diabetes. These investigators failed to demonstrate any difference in hepatic glucose release between control volunteers and subjects with type 2 diabetes, despite the fact that the overall glucose release (measured isotopically) was increased in the diabetic subjects. At face value, one might conclude that the discrepancy between increased overall glucose release and normal hepatic glucose release could have been caused wholly by increased renal glucose release. But the small number of subjects studied may have provided insufficient statistical power to demonstrate an increase in hepatic glucose release. Our own studies (76,77) have clearly demonstrated an increase in hepatic glucose release in hyperglycemic patients with types 1 and 2 diabetes.

Because acidosis increases renal gluconeogenesis but impairs hepatic gluconeogenesis (79), it is tempting to speculate that the kidney may be a major factor in accelerating gluconeogenesis in diabetic ketoacidosis. Moreover, one wonders to what extent the failure to suppress endogenous glucose release postprandially in diabetic patients (80) might involve an exaggerated increase in renal glucose release.

Interestingly, both of the above combined isotopic–net balance studies demonstrated that renal glucose uptake was increased in the diabetic subjects. These observations could explain the accumulation of glycogen found in diabetic kidneys (81). Therefore, some of the increased renal glucose release found in patients and animals with diabetes may be caused by increased renal glycogenolysis.

**CONCLUSIONS** — Recent studies indicate that the human kidney both consumes and releases glucose in the postabsorptive state and that, consequently, it is no longer appropriate to equate hepatic glucose release with overall systemic glucose release measured isotopically. It appears that the kidney may be roughly as important a gluconeogenic organ as the liver. Renal glucose release and uptake are under hormonal control. The kidney plays a role in human glucose counterregulation, can compensate at least partially for impaired hepatic glucose release, and contributes to the excessive glucose release seen in both types 1 and 2 diabetes. Further studies are needed to arrive at a consensus on the contribution of the kidney to overall glucose release; to evaluate the

effects of substrate availability, pharmacological agents, and additional hormones on renal glucose release; and to assess the role of the kidney in various pathological conditions (e.g., renal insufficiency, hepatic failure, sepsis, and aging).

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