Review

Bench-to-bedside review: Glucose production from the kidney

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Abstract

Data obtained from net organ balance studies of glucose production lead to the classic view according to which glucose homeostasis is mainly ensured by the liver, and renal glucose production only plays a significant role during acidosis and prolonged starvation. Renal glucose release and uptake, as well as the participation of gluconeogenic substrates in renal gluconeogenesis, were recently re-evaluated using systemic and renal arteriovenous balance of substrates in combination with deuterated glucose dilution. Data obtained using these methods lead one to reconsider the magnitude of renal glucose production as well as its role in various physiological and pathological circumstances. These findings now conduce one to consider that renal gluconeogenesis substantially participates in postabsorptive glucose production, and that its role in glucose homeostasis is of first importance.

Keywords Cori cycle, glucose homeostasis, glutamine, hypoglycemia, renal gluconeogenesis

Data obtained from net organ balance studies of glucose production lead to the classic view according to which glucose homeostasis is mainly ensured by the liver. Hence, these studies concluded that renal glucose production only plays a significant role during acidosis and prolonged starvation. These data were not in accordance with some clinical and biochemical evidence.

As a matter of fact, blood flow and gluconeogenic-enzyme equipment in the renal cortex are compatible, with a gluconeogenic activity similar to that of the liver [1]. Moreover, renal failure was shown to be the first cause of hypoglycemia after insulin therapy [2], suggesting the importance of this organ in blood glucose regulation.

The magnitude of renal glucose release and its role in various physiological and pathological circumstances were recently reconsidered in the light of new data on renal glucose release and uptake obtained by the combination of systemic and renal glucose arteriovenous balance and deuterated glucose dilution. These data now conduce one to consider that renal gluconeogenesis substantially participates in postabsorptive glucose production and that its role in adaptation is of first relevance. The present paper refers to recently published reviews on this topic [1,3].

Hepatic and renal gluconeogenesis in the postabsorptive phase

Glucose oxidation accounts for 50% of energy expenditure during the postabsorptive phase. Eighty percent of glucose utilization is located in insulin-insensitive tissues (mainly the brain) and the remaining 20% in insulin-sensitive tissues. Glucose requirements after an overnight fast are ensured by endogenous glucose production, which is approximately 10–11 μmol/kg/min [1]. According to data obtained from net organ balance studies of glucose production, the liver was considered the quasi-exclusive site of glucose production. As a matter of fact, net renal balance of glucose studies in healthy humans showed little or no net glucose release by the kidneys [4–6]. As a consequence, hepatic glucose production was considered to be ensured by hepatic glycogenolysis (75%) and by gluconeogenesis (25%) [7].

New data have been obtained during the past 5 years concerning the proportion of postabsorptive glucose release due to glycogenolysis and gluconeogenesis, on one hand, and the respective participation of the liver and the kidney due to gluconeogenesis, on the other. Different to the liver, the kidney does not contain a substantial amount of glycogen in healthy subjects. While the liver produces glucose from both glycogenolysis and gluconeogenesis, therefore, gluconeogenesis accounts for the whole renal glucose release.

The magnitude of postabsorptive glycogenolysis was recently re-evaluated using measurements of liver glycogen content by nuclear magnetic resonance [8]. These studies showed that glycogenolysis accounted for 45% of hepatic glucose release, instead of the earlier determined 25%. These findings were in accordance with the report that overall glucose release due to gluconeogenesis, as calculated from the isotopic dilution method, accounts for 54% of overall glucose release [9].

The relative contribution of the liver and the kidney to postabsorptive gluconeogenesis were recently re-evaluated. According to carbohydrate metabolism, the kidney can be considered as two distinct organs: the medulla, which is poorly vascularized and which is a site of glycolysis; and the cortex, which is a gluconeogenic organ [10]. The net organ balance of glucose thus does not reflect renal glucose release, but the difference between renal glucose release (mainly by the cortex) and renal glucose uptake (mainly by the medulla).

Glucose renal release was recently calculated using net renal glucose balance together with deuterated glucose dilution. These data, reviewed by Gerich *et al*. [1], showed that renal glucose release was responsible for a mean of 20% of endogenous glucose release [11–21]. As a consequence, one may now consider that postabsorptive systemic glucose release is ensured by hepatic glycogenolysis (50%), by hepatic gluconeogenesis (30%) and by renal gluconeogenesis (20%) (Fig. 1).

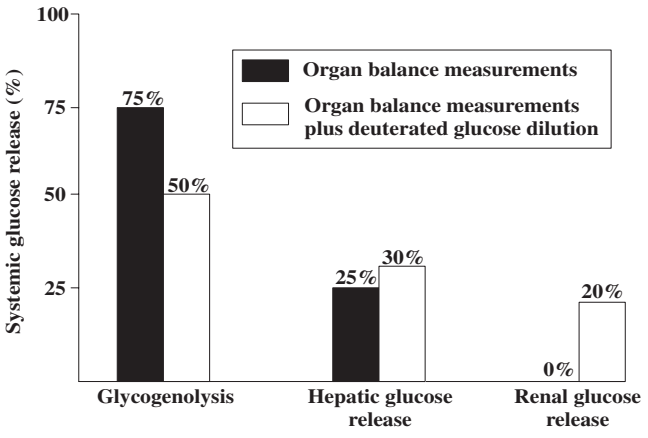
These data are in accordance with the report that, during liver transplantation in humans [22], glucose release represents 36% of basal levels 10 min after removal of the liver. Furthermore, Joseph *et al*. showed that extra-hepatic glucose release reached 54% of basal levels after 60 min. Such an increase of glucose release during the absorptive phase was associated with an increase in plasma counter-regulatory hormones and with a stabilization of the plasma levels of gluconeogenic substrates, particularly lactate and glycerol.

Substrates of renal gluconeogenesis

The main precursor for renal gluconeogenesis is lactate, followed by glutamine and glycerol [1]. The renal uptakes of these three substrates were recently reported to be 2.4 ± 0.5, 0.7 ± 0.2 and 0.6 ± 0.3 μmol/kg/min [20]. Table 1 presents the substrate contribution to renal gluconeogenesis as measured using arteriovenous renal glucose and substrate balances together with renal glucose release measurement using deuterated glucose dilution. According to these data, lactate accounted for approximately 50% of renal gluconeogenesis. It can be calculated that renal glucose release from lactate is equivalent to 50% of overall lactate conversion to glucose [1]. These data underline the major role of the kidneys in the Cori cycle (Fig. 2). One-half of glucose production within the Cori cycle actually takes place in the kidney.

Recent studies were devoted to the participation of amino acids in renal glucose production. During the postabsorptive phase, glutamine and alanine incorporation to renal gluconeogenesis was reported to respectively account for 73 and 4% of their overall incorporation into glucose [15]. These findings clearly demonstrate that gluconeogenesis from glutamine occurs primarily in the kidney, whereas gluconeogenesis from alanine mainly occurs in the liver. The determinism of such organ selectivity deserves some comments. Differences in

Figure 1



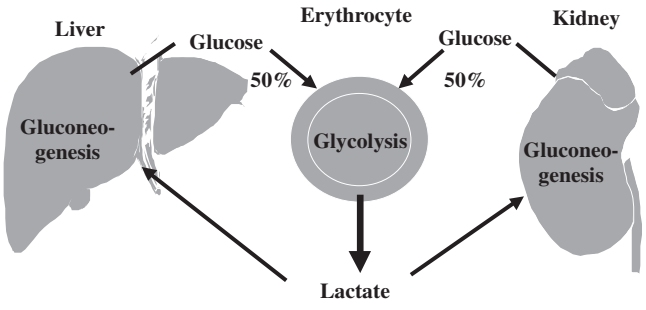
Renal glucose production measured using renal glucose balance or renal glucose balance together with deuterated glucose dilution. Data from [1].

Table 1

Renal gluconeogenic substrates determined using arteriovenous renal glucose and substrate balance together with renal glucose release measurement using deuterated glucose dilution

	% of renal glucose release				
Reference	Lactate	Glycerol	Glutamine	Alanine	Unknown
[1]	55	17	13	4	11
[19]		15			
[20]	40	10	20	0	40

Figure 2



Renal contribution to endogenous glucose release from lactate during the postabsorptive phase. Data from [1].

substrate availability may explain the variations of gluconeogenesis sources from one organ to another. Glutamine is thus largely taken up by the kidneys (60% of postabsorptive renal amino acid uptake [23]), while in the splanchic bed glutamine is first taken up by the intestine, which releases alanine in the portal stream [24].

It was more recently suggested that differences in amino acid transport in each organ may also influence the sources of gluconeogenesis [20]. As a matter of fact, glutamine transport depends on the A amino acid transport system in tubular cells and on the N system in hepatocytes [25]. As the A system but not the N system is under the control of insulin, glucagon and catecholamines [26], the aptitude of renal gluconeogenesis to respond to hormone stimulation may be greater than that of liver gluconeogenesis. Moreover, one can consider that renal gluconeogenesis from glutamine released by the muscle realizes a glutamine–glucose cycle similar to the alanine–glucose cycle involving the muscle and the liver [3].

Adaptation of gluconeogenesis

Hormone regulation

The effect of physiological hyperinsulinemia was assessed during hyperinsulinemic euglycemic clamp experiments in normal volunteers using organ balance measurement techniques in combination with an isotopic tracer [14]. In the kidney, insulin infusion (0.6 mU/kg/min) induced a reduction by 60% of glucose release and gluconeogenesis from glutamine. In the liver, glucose release and gluconeogenesis from glutamine were only decreased by 48 and 23%, respectively. Insulin increased systemic glutamine release, uptake, and clearance but did not affect renal glutamine uptake and release, suggesting that renal glutamine oxidation was increased [14].

Liver gluconeogenesis and glycogenolysis, and renal gluconeogenesis were studied using a similar experimental protocol [21]. During a 180-min insulin infusion (0.25 mU/kg × min), a rapid (30 min) suppression of endogenous glucose production was observed. Such an early decrease of endogenous glucose release was due to the simultaneous inhibition of liver glycogenolysis and renal gluconeogenesis. Hepatic gluconeogenesis decreased later (120–180 min). Considering the effect of insulin infusion on gluconeogenic substrates in each organs, it was observed that the net renal uptake of lactate decreased earlier (30 min) than the splanchnic uptake of lactate and alanine (120–180 min), and that both renal and splanchnic glycerol uptake decreased after 90 min of insulin infusion [21].

It can be deducted from these two studies that renal gluconeogenesis is more sensitive to insulin than liver gluconeogenesis. Moreover, these data underlined the role of decreased lactate uptake in the rapid decrease of renal glucose release in response to insulin infusion.

Glucagon was shown to increase systemic and hepatic glucose release but to have no effect on renal glucose release [16]. This effect of glucagon on glucose production was mainly attributed to an increase of gluconeogenesis from glutamine. During the infusion of glucagon, overall glucose production from glutamine and hepatic glucose production from glutamine were respectively increased by 36 and 280%, while renal glucose production from glutamine was unaffected.

Glucagon infusion may thus be an unusual circumstance during which substantial hepatic gluconeogenesis from glutamine may occur. It must be pointed out, however, that hepatic glucose release in these experiments was assumed to be equal to systemic glucose release minus renal glucose release. Consequently, one cannot exclude the participation of the gut, which was recently shown to contain the complete enzymatic equipment for gluconeogenesis [27,28], in extrarenal glucose production from glutamine.

Epinephrine infusion was conversely shown to induce a greater than twofold increase in systemic and renal glucose production, and to stimulate overall glutamine and alanine incorporation into glucose [15]. During a 2-hour infusion of epinephrine, different responses were observed in the kidney as compared with the liver: a sustained increase of renal glucose production was observed, whereas the hepatic response was transient.

The stimulation of systemic glucose production from glutamine was mainly related to renal gluconeogenesis (90% of total glutamine gluconeogenesis). The stimulation of alanine gluconeogenesis, on the contrary, only occurred in the liver [15]. The stimulation of renal gluconeogenesis during the epinephrine infusion may involve free fatty acids, the plasma concentrations of which were found to be increased during epinephrine infusion.

Starvation

As compared with the postabsorptive state, a 24-hour starvation state is characterized by a 60% decrease in both endogenous

glucose production and utilization. During such a fasting state, glycogen stores are depleted and glucose production only derives from gluconeogenesis. Studies using net glucose balance measurements reported that the liver accounted for 80–90% of glucose production, and the kidney for 10–20% [7].

The participation of the kidney to glucose production during starvation was recently investigated using the arteriovenous balance technique across kidneys and the splanchnic area combined with intravenous infusion of labeled glucose. These studies showed that, after 60 hours of fasting in healthy individuals, renal glucose production may account for 20–25% of whole-body glucose turnover [17]. The increase in fasting duration from 12 to 60 hours was associated with a 2.5-fold increase in renal glucose release while, in the same time, hepatic glucose release decreased by 25%. These data underline the role of the kidney in glucose homeostasis during starvation and explain the increased risk of hypoglycemia during renal failure [2].

Diabetes

Type 1 diabetes mellitus and type 2 diabetes mellitus are characterized by an increase in systemic, hepatic and renal glucose release [1]. In type 2 diabetes, a 300% increase in glucose release was reported in diabetics as compared with controls. This increment involved, in the same proportion, renal and hepatic glucose release [13].

It must be pointed out that renal glucose uptake was markedly increased during diabetes, resulting in a net renal glucose uptake. The fate of such an increase in glucose uptake by the kidney during diabetes is poorly known. It has been proposed that this glucose overload may contribute to the glycogen deposit that has been observed in these conditions [1]. In diabetic subjects [13], as in non-diabetic subjects [12,15], it was reported that renal glucose uptake was inversely correlated with free fatty acid uptake, suggesting the existence of a renal glucose–fatty acid cycle [12].

Renal gluconeogenesis during hypoglycemia

Hypoglycemia is frequent during chronic renal failure and has been attributed to multiple factors including abnormal liver gluconeogenesis [29]. However, the suppression of the role of the kidney in glucose homeostasis may be determinant. In healthy subjects, renal glucose release was studied in the postabsorptive phase and during a 180-min insulin clamp inducing either euglycemia or hypoglycemia [20]. As compared with euglycemia, hypoglycemia was associated with an 80% increase in systemic glucose release. During hypoglycemia, a 70% increase in renal glucose release, reaching 52.5% of endogenous glucose release, was observed.

This increase in renal gluconeogenesis during hypoglycemia was associated with an increase in the renal uptake of circulating gluconeogenic substrates. Plasma lactate, glycerol, and glutamine accounted for 30, 19 and 11%, respectively, of the increase of renal glucose release. These data suggest that the increase in renal gluconeogenesis from circulating substrates is integrated in the mechanism counteracting hypoglycemia [20]. It must be underlined that renal gluconeogenic precursors other than lactate, glutamine and glycerol represented 40% of renal gluconeogenesis. The participation of amino acids other than glutamine in renal gluconeogenesis, which has been reported in experimental acidosis [30,31], has not yet been investigated during hypoglycemia.

Conclusions

New data on renal glucose release and uptake obtained by the combination of systemic and renal glucose arteriovenous balance and deuterated glucose dilution make it possible to re-evaluate the role of the kidney in glucose homeostasis. Renal glucose release thus appeared to be of the same order of magnitude as splanchnic glucose release during the postabsorptive period. Furthermore, the peculiarity of renal glucose release appeared to be its sensitivity to hormone action, which gives the kidney a pre-eminent role in glucose homeostasis during various physiological and pathological states. Moreover, the reappraisal of renal gluconeogenesis together with studies on gluconeogenic substrates provided evidence for a key role of the kidney in interorgan glucose metabolism, and particularly in the Cori cycle and in gluconeogenesis from glutamine. These findings help the understanding of abnormal glucose homeostasis during chronic renal failure.

Competing interests

None declared.

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