Renal Compensation for Impaired Hepatic Glucose Release During Hypoglycemia in Type 2 Diabetes

Further Evidence for Hepatorenal Reciprocity

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During liver transplantation and after both meal ingestion and prolonged fasting, renal glucose release (RGR) increases while hepatic glucose release (HGR) decreases. These and other observations have led to the concept of hepatorenal reciprocity. According to this concept, reciprocal changes in hepatic and renal glucose release may occur to minimize deviations from normal glucose homeostasis. We further assessed this concept by testing the hypothesis that during counterregulation of hypoglycemia in patients with type 2 diabetes, whose glucagon responses to hypoglycemia (18–21) and, like those with type 1 diabetes, often have impaired glucagon responses to hypoglycemia (18–21), particularly as they approach the insulin-deficient end of the spectrum of type 2 diabetes (22). Although type 2 diabetic patients have been reported to have reduced hepatic glucose release during counterregulation of hypoglycemia (19), severe hypoglycemia is relatively uncommon in them compared with those with type 1 diabetes (16).

A potential explanation for this difference may be that type 2 diabetic patients have normal or increased epinephrine counterregulatory responses (18–21, 23) in contrast to type 1 diabetic patients who often have combined deficiencies of glucagon and epinephrine (2). Epinephrine is a potential explanation for this difference may be that type 2 diabetic patients have normal or increased epinephrine counterregulatory responses (18–21, 23) in contrast to type 1 diabetic patients who often have combined deficiencies of glucagon and epinephrine (2). Epinephrine is a
potent stimulator of renal glucose release (5,24). Intact or increased epinephrine counterregulatory responses in type 2 diabetic patients may thus promote increased renal glucose release and permit compensation for impaired hepatic glucose release. In patients with type 1 diabetes, hepatorenal reciprocity may not occur because decreased epinephrine counterregulatory responses prevent increased renal glucose release (25).

To date hepatic and renal glucose release during counterregulation of hypoglycemia in type 2 diabetes has not been evaluated. The present studies were undertaken to further assess the concept of hepatorenal reciprocity by testing the hypothesis that increased renal glucose release compensates for reduced hepatic glucose release during counterregulation of hypoglycemia in type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects. Informed written consent was obtained from 12 type 2 diabetic and 10 normal volunteers after the protocol had been approved by the University of Rochester Institutional Review Board. The type 2 diabetic subjects (10 men, 2 women) were 47 ± 2 years of age and weighed 100 ± 4 kg (BMI 31.4 ± 1.4 kg/m²). Their mean known duration of diabetes was 3.7 ± 0.5 years. Their HbA₁c and fasting plasma glucose were 7.2 ± 0.5 (27) in order to establish euglycemia for at least 2 h before the hypoglycemic overnight insulin infusion according to the algorithm by Mokan and Gerich purposes to be reported separately, subjects were also infused with [9,10-18528C]glucose at a rate of 0.1 mU·kg⁻¹·min⁻¹ in normal volunteers (65 ± 5 pmol/l, P < 0.001). However, during the hypoglycemic clamp, plasma insulin levels were not significantly different (452 ± 35 pmol/l in type 2 diabetic subjects and 381 ± 24 pmol/l in normal volunteers, P = 0.15). Baseline plasma C-peptide levels were significantly lower in type 2 diabetic subjects than in normal volunteers (373 ± 70 vs. 651 ± 37 pmol/l, P = 0.003). However, during the hypoglycemic clamp, plasma C-peptide levels were suppressed to comparable values (79 ± 10 vs. 90 ± 9 pmol/l in type 2 diabetic subjects and normal volunteers, respectively, P = 0.53), indicating similar suppression of endogenous insulin secretion and thus probably equivalent portal vein insulin levels.

Baseline plasma glucagon, cortisol, growth hormone, and norepinephrine concentrations in both groups were not significantly different (all P > 0.17). Baseline plasma epinephrine levels were greater in the type 2 diabetic subjects (306 ± 66 vs. 91 ± 10 pmol/l in the normal volunteers, P = 0.02). During the hypoglycemic clamp, plasma glucagon, cortisol, and norepinephrine increased comparably in both groups (all P > 0.32). Plasma epinephrine responses were nearly twofold greater in the type 2 diabetic subjects, averaging 2,162 ± 26 vs. 1,326 ± 193 pmol/l in the normal volunteers (P = 0.02). In contrast,
plasma growth hormone responses were lower in the type 2 diabetic subjects, averaging 3.5 ± 0.5 vs. 6.0 ± 0.6 ng/ml in normal volunteers (P = 0.01).

**Total, renal, and hepatic glucose release.** At baseline total endogenous glucose release (TEGR) was similar in type 2 diabetic subjects (10.8 ± 0.8 μmol · kg⁻¹ · min⁻¹) and in normal volunteers (11.0 ± 0.7 μmol · kg⁻¹ · min⁻¹, P = 0.37). During the hypoglycemic clamp, TEGR decreased initially to a comparable extent in both groups at 40 min, averaging 7.5 ± 0.6 and 7.9 ± 0.8 μmol · kg⁻¹ · min⁻¹ in the type 2 diabetic subjects and normal volunteers, respectively. Subsequently, despite ongoing hyperinsulinemia and coincident with increased secretion of counterregulatory hormones, TEGR increased in the normal volunteers but not in the type 2 diabetic subjects, averaging 10.2 ± 1.1 and 7.1 ± 0.6 μmol · kg⁻¹ · min⁻¹, respectively (P = 0.01) (Fig. 3).

Renal glucose release (RGR), which was nearly twofold higher in type 2 diabetic subjects at baseline (3.9 ± 0.3 vs. 2.1 ± 0.5 μmol · kg⁻¹ · min⁻¹, P = 0.01), decreased to comparable values between 40 and 80 min during the hypoglycemic clamp in both groups (1.8 ± 0.6 vs. 1.7 ± 0.5 μmol · kg⁻¹ · min⁻¹ in diabetic subjects and normal volunteers, respectively, P = NS). Subsequently, however, RGR increased in the type 2 diabetic subjects but continued to decrease for an additional 40 min in the normal volunteers to a nadir of 1.0 ± 0.8 μmol · kg⁻¹ · min⁻¹. During the last 90 min of the hypoglycemic clamp, RGR was nearly twofold greater in the type 2 diabetic subjects than in the normal volunteers, averaging 3.5 ± 0.6 vs. 1.8 ± 0.4 μmol · kg⁻¹ · min⁻¹, respectively (P = 0.015). Net renal glucose balance followed a pattern similar to that of renal glucose release: it was significantly more negative in the type 2 diabetic subjects at baseline (−214 ± 67 vs. −43 ± 25 μmol/min, P = 0.02); decreased to comparable nadirs at 80 min (−57 ± 55 vs. −44 ± 37 μmol/min; and during the last 90 min of the hypoglycemic clamp was nearly twofold more negative in the type 2 diabetic subjects (167 ± 38 vs. 89 ± 36 μmol/min, P = 0.049).

Hepatic glucose release (HGR) was lower but not significantly so at baseline in the type 2 diabetic subjects...
decreased progressively, averaging 3.9 HGR did not increase in the type 2 diabetic subjects, but P

**FIG. 3.** Total endogenous glucose release and rates of hepatic and renal glucose release.

(6.7 ± 0.7 vs. 8.9 ± 0.8 μmol · kg⁻¹ · min⁻¹ in normal volunteers, P = 0.09). During the hypoglycemic clamp, HGR did not increase in the type 2 diabetic subjects, but decreased progressively, averaging 3.9 ± 0.5 μmol · kg⁻¹ · min⁻¹. In normal volunteers, HGR decreased initially to a nadir of 4.9 ± 1.2 μmol · kg⁻¹ · min⁻¹ at 40 min and subsequently increased nearly twofold to rates averaging 8.6 ± 1.05 μmol · kg⁻¹ · min⁻¹, which was significantly greater than that in the type 2 diabetic subjects (P = 0.0015). During this period, HGR accounted for 83 ± 4% of TEGR in the normal volunteers, but only 54 ± 5% in the type 2 diabetic subjects (P = 0.0002).

**Plasma FFA concentrations and release and plasma lactate concentrations and renal net lactate balance.**

Renal blood flow was greater during the baseline period in the type 2 diabetic subjects (1,803 ± 140 vs. 1,368 ± 116 ml/min in the normal volunteers, P = 0.049) and remained greater during the hypoglycemic clamp (1,832 ± 134 vs. 1,272 ± 78 ml/min, P = 0.004). In the type 2 diabetic subjects there was a negative correlation at baseline between renal blood flow and renal glucose release (r = −0.72, P = 0.02). In contrast, during hypoglycemia, no correlation was found (r = 0.12, NS) (Fig. 4).

Plasma FFA concentrations, which were comparable at baseline (~560 μmol/l, P = 0.93) decreased during the hypoglycemic clamp to a lesser extent in the type 2 diabetic subjects (to 389 ± 36 vs. 228 ± 38 μmol/l in the normal volunteers, P = 0.004). Plasma FFA release followed a similar pattern as plasma FFA concentrations. Although baseline release was comparable in the type 2 diabetic subjects and the normal volunteers (4.3 ± 0.4 and 4.5 ± 0.6 μmol · kg⁻¹ · min⁻¹, respectively), there was overall less suppression of FFA release during the hypoglycemic clamp in the type 2 diabetic subjects with rates averaging 4.2 ± 0.7 vs. 2.4 ± 0.6 μmol · kg⁻¹ · min⁻¹ in the normal volunteers (P = 0.03).

Plasma lactate concentrations were significantly higher at baseline in the type 2 diabetic subjects (978 ± 55 and 680 ± 83 μmol/l in the normal volunteers, P = 0.01) and remained greater during the hypoglycemic clamp (P = 0.01). Net renal lactate uptake in type 2 diabetic subjects was greater at baseline (423 ± 54 vs. 200 ± 19 μmol/min in normal volunteers, P = 0.003) and during hypoglycemia (509 ± 67 vs. 293 ± 46 μmol/min in the normal volunteers, P = 0.03). During hypoglycemia, net renal lactate uptake was significantly correlated with renal glucose release (r = 0.6, P = 0.01).

**DISCUSSION**

The present studies were undertaken to further assess the concept of hepatorenal reciprocity (15). For this purpose we used counterregulation of hypoglycemia in type 2 diabetes as a model by testing the hypothesis that there would be increased renal glucose release to compensate for reduced hepatic glucose release, which had been previously reported (19) and would be anticipated to occur because of reduced hepatic glycogen stores (17) and impaired plasma glucagon counterregulatory responses in these patients (18–21).

During hypoglycemic clamp experiments, under conditions in which plasma glucose and insulin levels were comparable in type 2 diabetic subjects and normal volunteers, total endogenous glucose release was reduced ~30% in subjects with type 2 diabetes, as has been previously reported (19). Hepatic glucose release decreased progressively in the type 2 diabetic subjects and averaged only 45% of that of the normal volunteers. In contrast, renal glucose release in the type 2 diabetic subjects was increased approximately twofold compared with that in the normal volunteers and accounted for 46 ± 5% of total endogenous glucose release versus 17 ± 4% in the normal volunteers (P = 0.0002). Although this increase in renal glucose release only partially compensated for impaired hepatic glucose release, if renal glucose release had been reduced to the same degree as hepatic glucose release, total endogenous glucose release in the diabetic subjects would have been ~4.8 instead of 7.1 μmol · kg⁻¹ · min⁻¹. These observations provide further support for the concept of hepatorenal reciprocity, i.e., reciprocal changes in hepatic and renal glucose release may occur to minimize deviations from normal glucose homeostasis.

An important element in the renal compensation in type 2 diabetes observed in the present study seemed to be the increased plasma epinephrine responses. These responses could have promoted greater renal glucose release via several mechanisms. Firstly, they may have acted directly on the kidney via adrenergic receptors (41). Secondly, they may have acted indirectly via increasing plasma FFA...
concentrations due to stimulation of lipolysis. Plasma FFA concentrations were greater in our type 2 diabetic subjects during hypoglycemia, and FFAs are known to stimulate renal glucose release (42). Thirdly, they may have acted via increasing availability of lactate, the major gluconeogenic precursor (43), due to stimulation of glycogenolysis (18). Plasma lactate concentrations were greater in our type 2 diabetic subjects during hypoglycemia and increases in plasma lactate would provide more substrate of renal gluconeogenesis. Indeed, the increase in net renal lactate uptake in our diabetic subjects could have accounted for nearly 70% of their increased renal glucose release. Finally, although renal glucose release normally is almost exclusively due to gluconeogenesis (8), glycogen accumulates in kidneys of type 2 diabetic patients (44). Therefore, part of the compensatory increase in renal glucose release observed in our type 2 diabetic subjects may have been the result of epinephrine stimulation of renal glycogenolysis.

The increased epinephrine responses in the type 2 diabetic subjects noted in our and other studies (18–21,23) are likely the result of the shift in the glycemic threshold for their response to a higher plasma glucose level known to occur in type 2 diabetes (23,45). If, as our results suggest, increased plasma epinephrine responses in patients with type 2 diabetes permitted renal compensation for impaired hepatic glucose release, one would predict that this would not be possible in patients with type 1 diabetes who have reduced plasma epinephrine responses. Indeed, it has recently been reported (25) that patients with type 1 diabetes have reductions in both renal and hepatic glucose release during hypoglycemia. Thus, lack of renal compensation due to impaired epinephrine responses could explain at least in part the differences in propensity for severe hypoglycemia in type 1 diabetes and type 2 diabetes (16).

Another clinical implication of our findings relates to the propensity of type 2 diabetic patients for severe hypoglycemia when they develop end-stage renal disease (8,46,47). Although this no doubt has a complex etiology, involving such factors as decreased insulin degradation, reduced drug clearance, poor nutrition, etc. (8,47), a further factor to be considered on the basis of our results would be loss of the compensatory increase in renal glucose release during counterregulation of hypoglycemia.

We had expected that the reduction of hepatic glucose release found in our type 2 diabetic subjects would be explained at least in part by reduced plasma glucagon responses. However, this was apparently not the case since plasma glucagon responses to hypoglycemia were not significantly different in our type 2 diabetic subjects and normal volunteers. The lack of decreased counterregulatory glucagon responses in our subjects versus several previous reports (18–21) might be related to the relative short duration of diabetes in our subjects (average <4 years) compared with those in studies finding a reduction in counterregulatory glucagon response in type 2 diabetes. Indeed, Segel et al. (22) found markedly reduced glucagon responses in patients with advanced type 2 diabetes (i.e., those requiring long-term therapy with insulin) but not in those still effectively managed with oral agents similar to those studied here.

There are, however, other possible explanations for the decreased hepatic glucose release. Plasma growth hormone responses were reduced in our type 2 diabetic subjects, as has been previously reported (48). This may have played a role since growth hormone promotes hepatic glucose release (3). More importantly, perhaps, hepatic glycogen stores are now known to be reduced in type 2 diabetes (17), and glucagon activation of hepatic membrane adenylate cyclase has also been found to be reduced in type 2 diabetes (49). These changes would be expected to impair hepatic glycogenolytic and gluconeogenic responses to glucagon. Finally, although increases in plasma FFAs may increase gluconeogenesis (42), recent studies indicate they may reduce hepatic glycogenolysis (50). Thus, the greater plasma FFA concentrations found in our type 2 diabetic subjects during hypoglycemia may have
reduced hepatic glycogenolysis while increasing renal gluconeogenesis.

It should be noted that four of the type 2 diabetic subjects had been treated with metformin. Although medication was discontinued 4 days before study, some residual effect may have persisted. Metformin has been shown to reduce hepatic gluconeogenesis in vitro (51) and the incorporation of lactate into glucose in humans (34). There are no data regarding the effect of metformin on human renal gluconeogenesis, but a differential action of the drug on liver and not kidney theoretically could have influenced our results and explain why hypoglycemia is generally not observed when this drug is used as monotherapy. Nevertheless, since hepatic and renal responses observed in our subjects treated with metformin did not differ from those not treated with it, an influence of antecedent metformin treatment on our results seems unlikely.

The present studies were undertaken to test the overall concept of hepatorenal reciprocity and not to quantitatively compare renal and hepatic glucose release. As previously discussed (8,29,37), calculation of renal glucose release involves numerous simultaneous measurements (e.g., small arteriovenous differences in plasma glucose concentration and specific activity as well as large renal blood flows), which can make precise quantification difficult. Thus, rates of renal glucose release need to be interpreted with caution. Similarly, although kidney and liver are the only organs able to release glucose into the circulation, calculation of hepatic glucose release as the difference between total endogenous glucose release and renal glucose release is subject to the same imprecision. Overestimation of renal glucose release will of necessity result in an underestimation of hepatic glucose release.

Both liver and kidney simultaneously take up and release glucose, necessitating the use of combined net balance and isotopic techniques to measure release. Net glucose balance represents the difference between uptake and release of glucose by these organs. Although net glucose release by the kidney was increased in the type 2 diabetic subjects during hypoglycemia in the present study, it underestimates the actual amount of glucose released by the kidney into the circulation (i.e., the contribution of the kidney to total endogenous glucose release) to the extent that there was simultaneous glucose uptake by the kidney.

In conclusion, the present studies indicate that in patients with type 2 diabetes, renal glucose release increases to compensate partially for reduced hepatic glucose release during counterregulation of hypoglycemia. These observations thus provide additional support for the concept of hepatorenal reciprocity. Renal compensation for impaired hepatic glucose release may explain at least in part the difference in prevalence of severe hypoglycemia in type 1 diabetes and type 2 diabetes. Loss of this renal compensation in type 2 diabetic patients with renal insufficiency may contribute to their propensity for severe hypoglycemia.

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REFERENCES

HEPATORENAL GLUCOSE RECIPROCITY