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, who would be expected to have reduced HGR, RGR would be increased. Accordingly, we performed hypoglycemic hyperinsulinemic clamp experiments (~3.1 mmol/l) in 12 type 2 diabetic and in 10 age-weight–matched nondiabetic volunteers and measured total endogenous glucose release (TEGR) and RGR using a combined isotopic net balance approach. HGR was calculated as the difference between TEGR and RGR since only these organs are capable of releasing glucose. We found that during comparable hypoglycemia and hyperinsulinemia, TEGR was reduced in type 2 diabetes (6.6 ± 0.6 vs. 10.2 ± 1.1 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ in nondiabetic volunteers, $P = 0.01$) due to reduced HGR (3.9 ± 0.5 vs. 8.6 ± 1.0 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ in nondiabetic volunteers, $P = 0.0015$). In contrast, RGR was increased approximately twofold in type 2 diabetes (3.3 ± 0.5 vs. 1.6 ± 0.3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ in nondiabetic volunteers, $P = 0.015$). Plasma epinephrine, lactate, and free fatty acid concentrations, which would promote RGR, were also greater in type 2 diabetes (all $P < 0.01$). Our results provide further support for hepatorenal reciprocity and may explain at least in part the relatively low occurrence of severe hypoglycemia in type 2 diabetes compared with type 1 diabetes where both HGR and RGR counterregulatory responses are reduced. *Diabetes* 52:1386–1392, 2003

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FFA, free fatty acid; FX, fractional extraction; HGR, hepatic glucose release; NB, net balance; RBF, renal blood flow; RGR, renal glucose release; RPF, renal plasma flow; RGU, renal glucose uptake; TEGR, total endogenous glucose release.

Hypoglycemia impairs cerebral function and can cause death. It is therefore not surprising that an elaborate system has evolved to protect the body against this threat (1). The key element in this defense is an increase in secretion of counterregulatory hormones (glucagon, epinephrine, growth hormone, and cortisol) when plasma glucose levels decrease below a certain threshold (2,3). These hormones act primarily by increasing glucose release and, to a lesser extent, by limiting glucose utilization (4).

The increased release of glucose during counterregulation of hypoglycemia in humans has generally been thought to be solely the result of hepatic glucose release (1). However, several studies in humans (5–7) have now confirmed observations in animals (8) that both liver and kidney increase their glucose release during hypoglycemia. Based on these and other studies (9–14), a concept has emerged, referred to as hepatorenal reciprocity (15). According to this concept, reciprocal changes may occur in renal and hepatic glucose release to maintain normoglycemia.

For example, during hepatic transplant surgery (9–11), when patients are without a liver, the kidney increases its release of glucose and compensates for lack of hepatic glucose release so that little or no exogenous glucose is needed to maintain normoglycemia. This renal compensation for impaired hepatic glucose release may thus explain why hypoglycemia is relatively infrequent in patients with severe liver disease (1,12).

An even more common clinical condition in which hepatorenal reciprocity may be operative is the counterregulation of hypoglycemia in patients with type 2 diabetes (16). These patients have reduced hepatic glycogen stores (17) 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

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/m^2). Their mean known duration of diabetes was 3.7 ± 0.5 years. Their HbA_{1c} and fasting plasma glucose were 7.2 ± 0.3 and 7.8 ± 0.5 mmol/l, respectively. None acknowledged a hypoglycemic episode within the past 2 weeks. Three subjects had been treated with metformin alone; three had been treated with metformin plus a sulfonylurea; two were on a sulfonylurea alone; one was treated with metformin plus bedtime NPH insulin; one subject was treated with repaglinide; and two were treated with diet alone. Two of the 12 diabetic subjects had mild hypertension that had been treated in one instance with a calcium channel blocker and in the other with a β-blocker. These medications had been discontinued 4 days before study. The normal volunteers (eight men, two women) were 43 ± 2 years of age and weighed 93 ± 3 kg (BMI 31.7 ± 1.4 kg/m^2) and had normal glucose tolerance (World Health Organization criteria) (26), as well as no family history of diabetes. All subjects had normal physical examinations and routine laboratory tests. For 3 days before the study, all had been on a weight-maintaining diet containing at least 200 g carbohydrate and had abstained from use of alcohol.

Protocol. Subjects were admitted to the University of Rochester General Clinical Research Center between 6:00 and 7:00 P.M. the evening before experiments, consumed a standard meal between 6:30 and 8:00 P.M., and fasted thereafter until experiments were completed. Diabetic subjects received an overnight insulin infusion according to the algorithm by Mokan and Gerich (27) in order to establish euglycemia for at least 2 h before the hypoglycemic clamp experiment. The insulin infusion (~0.1 mU · kg^{-1} · min^{-1}) needed for this was continued throughout the experiment.

At ~5:00 A.M. a primed-continuous infusion of [6-^{3}H]glucose (~30 μCi, ~0.3 μCi/min; Amersham International, U.K.) were started in all subjects. For other purposes to be reported separately, subjects were also infused with [9,10-^{3}H]palmitate (~0.2 μCi/min; Amersham International) and [U-^{14}C]glutamine (~20 μCi, ~0.2 μCi/min; Amersham International). At ~8:00 A.M., an infusion of *p*-aminohippuric acid (12 mg/min) was started for determination of renal blood flow. Between 8:00 and 9:00 A.M., the right renal vein was catheterized under fluoroscopy and the position of the catheter tip ascertained by injecting a small amount of iodinated contrast material. At ~9:00 A.M., a dorsal hand vein was cannulated and kept in a thermoregulated Plexiglass box at 65°C for sampling arterialized venous blood. About 1 h later, three blood samples were collected simultaneously from the dorsal hand vein and the renal vein at 30-min intervals (−60, −30, 0 min) for determination of glucose, lactate, insulin, glucagon, cortisol, growth hormone, epinephrine, norepinephrine, and *p*-aminohippuric acid concentrations and for determination of [^{3}H]glucose and palmitate specific activities by previously described methods (28–34). At 0 min, the infusion of insulin was increased to ~0.82 mU · kg^{-1} · min^{-1} in the type 2 diabetic subjects; in normal volunteers insulin was infused at a rate of 0.78 mU · kg^{-1} · min^{-1}. Subsequently, plasma glucose concentrations were allowed to decrease to ~3.2 mmol/l. Plasma glucose levels were clamped at this level with infusion of exogenous 20% glucose, as needed, enriched with [6-^{3}H]glucose to minimize alteration in specific activities that might lead to underestimation of glucose rates of appearance (35,36). Blood was collected as described above at 30- to 40-min intervals.

Calculations. Assumptions and methodologic limitations of the combined net balance and isotopic approach for determining glucose release by liver and kidney have been previously discussed in detail (8,29,37). Systemic (overall) glucose and palmitate release were calculated with steady-state equations under basal conditions (38) and subsequently during clamp experiments with non–steady-state equations (36,39). Because palmitate represents 31% of total plasma free fatty acids (FFAs) (34), systemic palmitate release was divided by 0.31 to extrapolate data to total FFAs. Renal plasma flow (RPF) was determined by the *p*-aminohippuric acid clearance technique (31), and renal blood flow (RBF) was calculated as RPF/(1 − Hematocrit). Renal glucose fractional extraction (FX) was calculated as (arterial [6-^{3}H]glucose specific activity × arterial glucose concentration − renal vein [6-^{3}H]glucose specific activity × renal vein glucose concentration)/(arterial glucose specific activity × arterial glucose concentration). Renal glucose uptake (RGU) was calculated as RBF × arterial glucose concentration × FX. Renal glucose net balance (NB) was calculated as RBF × (arterial glucose concentration − renal vein glucose concentration). Renal glucose release was calculated as RGU − NB. Renal net balance of lactate was calculated as described above for glucose. Hepatic glucose release was calculated as the difference between the systemic glucose release and renal glucose release. Negative values for fractional extraction and glucose release, which were occasionally encountered, were treated as negative values.

Statistical analysis. Unless stated otherwise, data are expressed as means ± SE. Unless otherwise specified, paired two-tailed Student's *t* tests were used to compare the average of data obtained from baseline with the mean of data obtained from the last 160 min of the hypoglycemic clamp experiments since stable hypoglycemia was achieved during this period. In two of the subjects, the renal vein catheter was displaced during the experiments so that hormonal responses are based on all subjects, but renal glucose release and hepatic glucose release are based on 10 subjects. Baseline data from 10 of the 12 diabetic subjects and those of all the nondiabetic volunteers have been included in a previous publication (40). Unpaired two-tailed Student's *t* tests were used to compare data between the groups. A P value <0.05 was considered statistically significant.

RESULTS

Arterial glucose and hormone concentrations. After overnight infusion of insulin, plasma glucose concentrations in type 2 diabetic subjects were comparable to those of normal volunteers (5.3 ± 0.1 and 5.2 ± 0.1 mmol/l, respectively, $P = 0.4$). During the hypoglycemic clamp, plasma glucose decreased similarly in both groups, averaging 3.3 ± 0.1 and 3.2 ± 0.1 mmol/l during the last 160 min in type 2 diabetic subjects and normal volunteers, respectively ($P = 0.12$) (Figs. 1 and 2).

Baseline plasma insulin concentrations in the type 2 diabetic subjects (133 ± 21 pmol/l) were higher than in the 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,

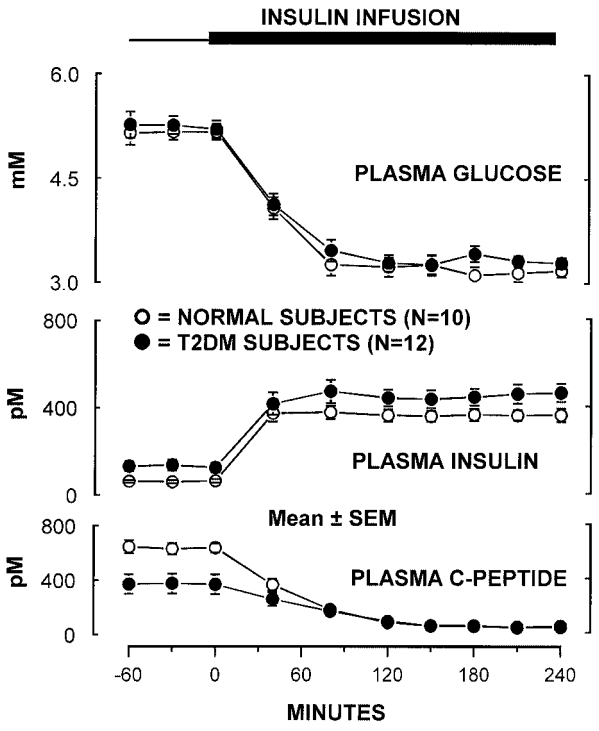

FIG. 1. Arterial glucose, insulin, and C-peptide concentrations.

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

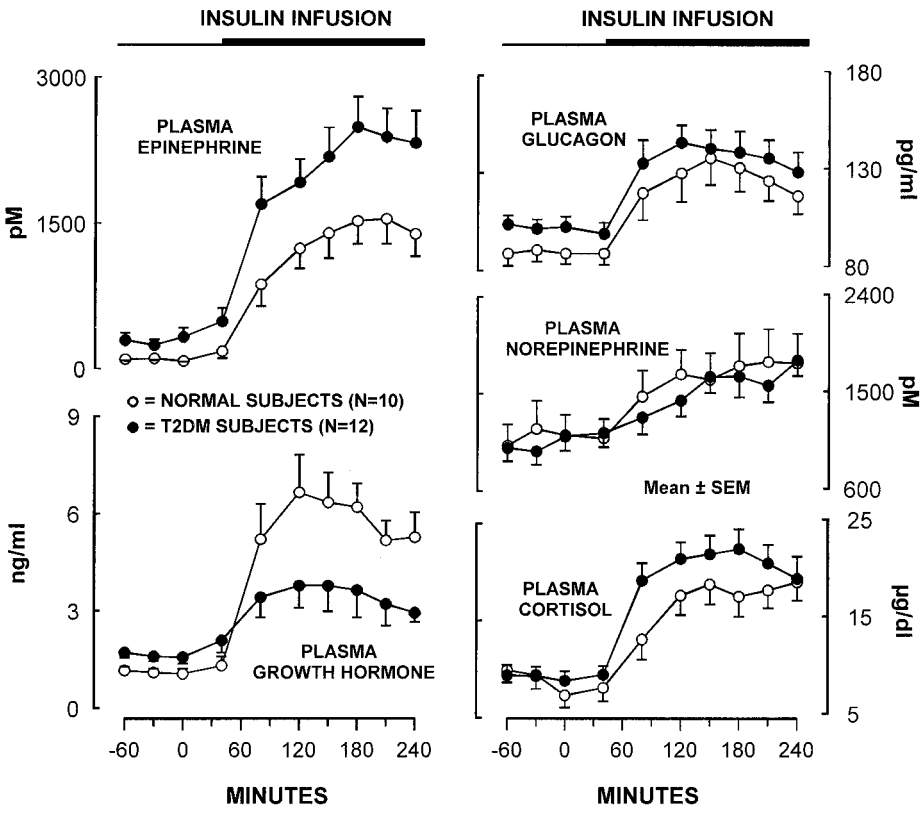

FIG. 2. Arterial counterregulatory hormone concentrations.

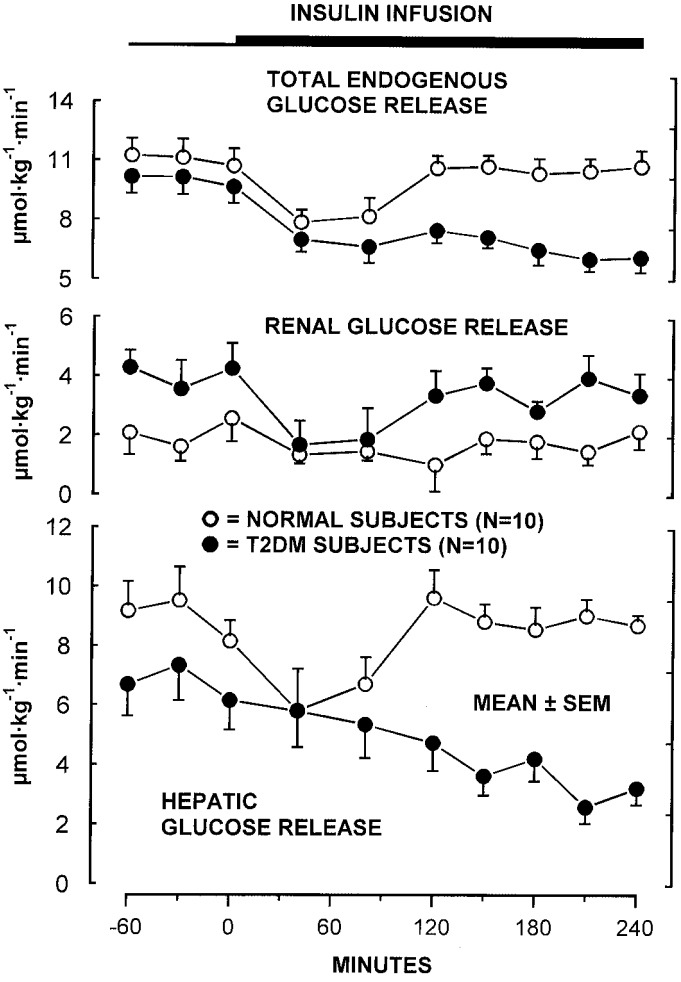

FIG. 3. Total endogenous glucose release and rates of hepatic and renal glucose release.

(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

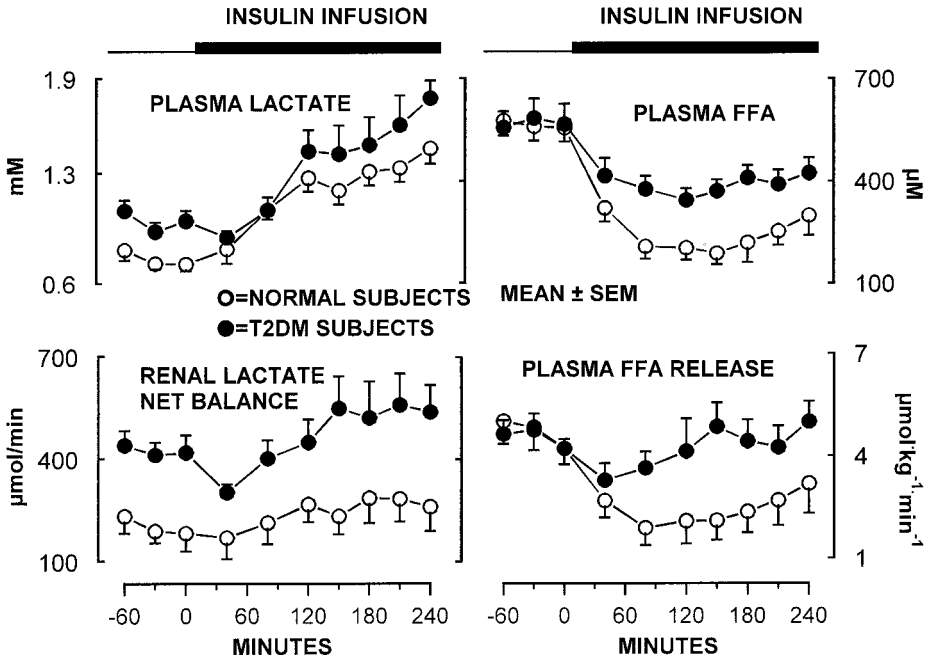

FIG. 4. Arterial FFA and lactate concentrations and renal lactate net release.

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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