Fructose Normalizes Specific Counterregulatory Responses to Hypoglycemia in Patients With Type 1 Diabetes

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We have previously reported that specific counterregulatory responses to hypoglycemia were augmented by an infusion of fructose in nondiabetic humans. We hypothesized that this effect was due to the interaction of a "catalytic" dose of fructose with the regulatory protein for glucokinase in glucose-sensing cells that drive counterregulation. To examine whether fructose could restore counterregulatory responses in type 1 diabetic patients with defective counterregulation, we performed stepped hypoglycemic clamp studies (5.0, 4.4, 3.9, and 3.3 mmol/l glucose steps, 50 min each) in eight intensively treated patients (HbA1c 6.4 ± 0.7%) on two separate occasions: without (control) or with confusion of fructose (1.2 mg · kg⁻¹ · min⁻¹). Fructose induced a resetting of the glycemic threshold for secretion of epinephrine to higher plasma glucose concentrations (from 3.3 ± 0.1 to 3.9 ± 0.1 mmol/l; P = 0.001) and markedly augmented the increment in epinephrine (by 56%; P < 0.001). The amplification of epinephrine responses was specific; plasma norepinephrine, glucagon, growth hormone, and cortisol were unaffected. Hypoglycemia-induced endogenous glucose production ([3−3H]-glucose) rose by 90% (P < 0.001) in the fructose studies, compared with −2.0% (NS) in control. In concert, the glucose infusion rates during the 3.9- and 3.3-mmol/l steps were significantly lower with fructose (2.3 ± 0.6 and 0.0 ± 0.0 vs. 5.9 ± 1.15 and 3.9 ± 1.0 μmol · kg⁻¹ · min⁻¹, respectively; P < 0.001 for both), indicating the more potent counterregulatory response during fructose infusion. We conclude that infusion of fructose nearly normalizes the epinephrine and endogenous glucose production responses to hypoglycemia in type 1 diabetic patients with impaired counterregulation, suggesting that defects in these responses may be dependent on glucokinase-mediated glucose sensing. Diabetes 54:609–616, 2005

Although many studies have demonstrated a beneficial effect of intensive glycemic control in patients with type 1 diabetes, such a therapeutic approach carries a significant risk for frequent and severe episodes of hypoglycemia (1,2). In fact, iatrogenic hypoglycemia is the limiting factor in the management of glycemia in people with type 1 diabetes (1).

The appropriate sensing of hypoglycemia and a closely coupled counterregulatory response represent the most important mechanisms responsible for recovery from hypoglycemia. Unfortunately, many patients with type 1 diabetes—and most of those on intensive therapy—display delayed and inadequate glucose recovery from hypoglycemia, as a result (at least in part) of defects in sensing low blood glucose and/or triggering appropriate neurohormonal counterregulatory responses (3). The latter are characterized by deficiencies of glucagon and epinephrine secretion, resulting in impaired activation of endogenous glucose production (EGP) that normally restores euglycemia (3–6). The mechanisms underlying the epinephrine defect are associated with repeated episodes of hypoglycemia and characterized by elevated glycemic thresholds for counterregulatory hormone secretion and decreased magnitude of counterregulatory hormone released (1,3–6). These hormonal defects—combined with impaired autoregulatory EGP responses (7)—lead to the markedly increased risk for severe hypoglycemia in intensively treated patients (8).

The physiological sensing of plasma glucose has been largely elucidated at the level of the pancreatic β-cell. After transport into the cell via the GLUT 2 system, glucose is phosphorylated into glucose 6-phosphate (G6P) by the rate-limiting enzyme glucokinase. Glucokinase plays an important role in the regulation of insulin secretion because of its specific kinetic characteristics: low affinity for glucose, cooperativity with glucose, and lack of feedback inhibition by its product, G6P. Thus, minimal fluctuations in blood glucose activate glucokinase with proportional formation of G6P, the first step in the glycolytic pathway (9). Consequently, the amount of G6P produced in the pancreatic β-cell determines the magnitude of insulin release (by increasing the ATP-to-ADP ratio, closing ATP-sensitive K⁺ channels (K_ATP channels), and causing membrane depolarization and a proportional influx of calcium into the cell, which ultimately induces insulin release [10,11]). Moreover, recent studies have demon-
In the liver, glucokinase activity is acutely regulated by its interaction with a glucokinase regulatory protein (GKRP), which is located within the nucleus and functions as an anchor (14). GKRP activity is enhanced by fructose 6-phosphate (F6P) and suppressed by fructose 1-phosphate (F1P). Thus, when fructose is phosphorylated via fructokinase (as demonstrated in the hepatocyte), the resulting F1P activates glucokinase. We hypothesized that under circumstances in which fructose is phosphorylated via a hexokinase to F6P (e.g., in neurons or glial cells), inhibition of glucokinase will result. Activation of glucokinase activity by fructose has been unequivocally demonstrated in the liver (14,15). This mechanism, however, is not proved in other glucose-sensing cells, such as the pancreatic β-cell. Nonetheless, because other key glucose-sensing cells are equipped with the same enzymatic systems (including glucokinase and GKRP), we hypothesized that fructose could modulate their activity.

The precise location(s) for hypoglycemia sensing has not yet been elucidated. In addition to areas in the brain such as the ventromedial hypothalamic nuclei and paraventricular nuclei, the hepatic portal system may play a role (12,16,17). It should be noted that these putative hypoglycemia-sensing tissues have been shown to possess the same cellular systems seen in the pancreatic β-cell (GLUT2, glucokinase, and KATP channels) (18–20), lending support to the hypothesis that these sites play an important physiological role in detection of hypoglycemia.

We reasoned that because fructose has been shown to have a catalytic effect on glucokinase activity, its effect could be exploited to examine the mechanisms of hypoglycemia sensing and glucose counterregulation in humans. Thus, we have previously demonstrated that the counterregulatory response to hypoglycemia can be augmented by an acute infusion of a “catalytic” low dose of fructose in nondiabetic humans. In these studies, the amplification of hypoglycemia counterregulation was characterized by activation of epinephrine and glucagon secretion and by concomitant—and possibly direct—amplification of increments in EGP (21).

In people who have type 1 diabetes and are on intensive therapy, it is not clear whether the defects in counterregulation are associated with alterations in glucokinase regulation or whether manipulation of glucokinase-dependent sensing mechanisms could override impaired counterregulatory systems. We therefore designed the present study to examine whether fructose infusion can restore the impaired counterregulatory responses to hypoglycemia in patients who have type 1 diabetes and experience defective counterregulation to hypoglycemia.

**RESEARCH DESIGN AND METHODS**

We studied eight patients with type 1 diabetes (five men and three women). They had a mean ± SE HbA1c of 6.4 ± 0.7%, an average age of 33.1 ± 6.5 years, and a mean BMI of 24.6 ± 3.5 kg/m². The average duration of diabetes was 9.3 ± 3.5 years. All patients were treated intensively with insulin. Except for diabetes, all were in general good health. Eligibility for the study was determined by history, physical examination, and hematological and biochemical tests. Individuals with clinical neuropathy, anemia, bleeding disorders, recent weight changes, or unstable metabolic control were excluded. Patients were instructed to avoid any episodes of hypoglycemia in the 2-week period before the studies. Informed written consent was obtained in accordance with the policy of the Committee on Clinical Investigations of the Albert Einstein College of Medicine.

Each patient participated in two stepped hypoglycemic clamp studies separated by an interval of 4–6 weeks. During each hypoglycemic clamp, patients received either fructose (1.2 mg · kg⁻¹ · min⁻¹) or saline intravenously in random order.

Long-acting insulin was withheld the morning before admission. Patients were admitted to the General Clinical Research Center the evening before the study for low-dose overnight insulin infusion to establish euglycemia by the morning of study. Beginning at 2:30 on the night before the study, patients were asked to fast, and a variable intravenous infusion of insulin was started. The overnight insulin infusion rate was adjusted according to an algorithm based on hourly blood glucose measurements, ensuring a gradual normalization of plasma glucose levels. The experimental protocol was initiated the next morning.

At 0700 on the day of study, two indwelling canulae were inserted, one in an antecubital vein for infusions and the second placed in a retrograde manner in a distal hand vein of the contralateral forearm for blood sampling. For obtaining arterialized venous blood samples, this hand was maintained at 55°C in a thermoregulated Plexiglas box. At t = 0–120 min, a primed-continuous infusion of high-performance liquid chromatography–purified [3-3H]glucose (New England Nuclear, Boston, MA) was initiated with a bolus of 21.6 µCi followed by continuous infusion of 0.15 µCi/min for the entire period of study. The overnight activity of infused dextrose was kept equivalent to plasma glucose specific activity by addition of [3-3H]glucose to the infuse, using the method of Finegood et al. (22) to prevent negative R₂ artifacts. At t = 0 min, insulin infusion (Humulin Regular; Eli Lilly, Indianapolis, IN) was increased from baseline to a rate of 0.4 mU · kg⁻¹ · min⁻¹, and a variable infusion of 29% dextrose was begun to maintain the plasma glucose concentration at 5.0 mmol/l for 50 min (step 1 of the clamp). At t = +50 min and every 50 min thereafter, the plasma glucose concentration was decreased by 0.5 mmol/l decrements for 50 min each by reducing the dextrose infusion rate accordingly. The plasma glucose was clamped at the desired range by varying the dextrose infusion according to plasma glucose measured at 5-min intervals with targets of 4.4, 3.9, and 3.3 mmol/l. At t = +50 min (at a plasma glucose ~5.0 mmol/l), an infusion of fructose 1.2 mg · kg⁻¹ · min⁻¹ or saline was initiated and maintained constant until the end of the study. This infusion rate of fructose was selected to achieve plasma fructose levels of ~200 µmol/l (23,24). Such low-circulating levels of fructose would be regulatory for glucokinase translocation, without affecting directly the rates of EGP (25). At the end of the clamp, all of the infusions were discontinued, the patient resumed his or her usual insulin regimen, a meal was given, and the patient was discharged from the General Clinical Research Center.

Fasting blood for HbA1c was collected on the morning of each clamp study. During the clamps, blood samples were obtained for the determinations of plasma free insulin, glucagon, epinephrine, norepinephrine, cortisol, growth hormone, and glucose kinetics.

**Analytical methods.** Plasma glucose was measured with a Beckman glucose analyzer (Fullerton, CA), using the glucose oxidase method. Plasma [3-3H]glucose radioactivity was measured in duplicate on the supernatants of barium hydroxide–zinc sulfate precipitates of plasma samples, after evaporation to dryness to eliminate tritiated water. The methods for measurement of plasma insulin, glucagon, epinephrine, norepinephrine, cortisol, and growth hormone and their intra- and interassay variations have been previously reported (26).

**Analyses.** The data in the text, figures, and tables are presented as the means ± SE. Steele’s equation was used for calculation of glucose turnover as described elsewhere (27). Values for EGP and glucose uptake, obtained at 10 min after the glucose infusion was stopped, were averaged over the final 30 min of step 1 or saline was infused intravenously for the entire duration of step 1 for each individual patient. The glycemic thresholds for activation of counterregulatory hormone secretion was calculated as the glycemic level at which there was an increase of >2 SDs above the basal plasma hormone concentration (28,29). The area under the curve (AUC) was calculated using the trapezoidal method, for the whole duration of the clamp (29). Statistical analyses were performed using repeated-measures ANOVA for multiple comparisons and paired student’s t test for comparing means before and after the intervention (fructose infusion). P < 0.05 was considered significant.

**RESULTS**

Plasma glucose levels and glucose infusion rates. Plasma glucose concentrations at t = 0 were 5.1 ± 0.1 mmol/l in the fructose studies and 5.1 ± 0.2 mmol/l in the control studies (NS). No significant difference was noted between the fructose and control studies during the 5.0–
4.4-, and 3.9-mmol/l plasma glucose steps (4.9 ± 0.1, 4.5 ± 0.1, and 4.0 ± 0.2 mmol/l in the fructose studies and 5.1 ± 0.1, 4.4 ± 0.1, and 3.9 ± 0.1 mmol/l in control). However, during the 3.3-mmol/l plasma glucose step, there was a significantly higher plasma glucose concentration in the fructose compared with the control studies (4.1 ± 0.1 vs. 3.3 ± 0.1 mmol/l, respectively; *P* < 0.001; Fig. 1) because plasma glucose could not be lowered further as a result of the amplified counterregulatory responses. Plasma glucose levels in the fructose studies were higher during this glucose step despite that the glucose infusion was discontinued and coincided with elevated plasma concentration of epinephrine and a significant increase in EGP (see below). Thus, using the same insulin infusion rate (0.4 mU·kg⁻¹·min⁻¹) in the fructose and the control studies, plasma glucose could not be lowered to the desired glucose step in the fructose studies, suggesting greater activation of counterregulatory systems.

Glucose infusion rates in the experimental protocol are depicted in Fig. 2. During the first and second glucose steps, average glucose infusion rates were comparable in both studies (9.0 ± 1.3 μmol·kg⁻¹·min⁻¹ in the fructose and 9.1 ± 1.6 μmol·kg⁻¹·min⁻¹ in the control studies; NS). However, during the 3.9-mmol/l glucose step and the onset of hypoglycemia, the mean rate of glucose infusion was lower in the fructose studies (2.3 ± 0.6 vs. 5.9 ± 1.2 μmol·kg⁻¹·min⁻¹ in the fructose and 9.1 ± 1.6 μmol·kg⁻¹·min⁻¹ in the control studies; NS). Further reduction in plasma glucose to 3.9 mmol/l was associated with an increment in plasma epinephrine in

**Counterregulatory hormones.** During the 5.0- and 4.4-mmol/l glucose steps, plasma epinephrine concentrations remained near basal values and were comparable in both fructose and control studies (604 ± 187 pmol/l with fructose and 570 ± 166 pmol/l without fructose; NS; Table 1). Further reduction in plasma glucose to 3.9 mmol/l was associated with an increment in plasma epinephrine in
both sets of studies, although the threshold for epinephrine release occurred at a higher plasma glucose concentration in the fructose compared with the control studies (3.9 ± 0.1 vs. 3.3 ± 0.1 mmol/l, respectively; P < 0.001; Fig. 4A). Furthermore, the mean maximal increment in plasma epinephrine was also significantly higher during the 3.9- and 3.3-mmol/l glucose steps in the fructose compared with the control studies, averaging 1,267 ± 206 vs. 1,013 ± 180 pmol/l, respectively, during the 3.9-mmol/l glucose step and 2,940 ± 360 vs. 1,880 ± 168 pmol/l, respectively, during the 3.3-mmol/l glucose step (both P < 0.001). The AUC for epinephrine during the entire duration of the clamps was also significantly greater in the fructose compared with control studies (2,873 ± 188 vs. 1948 ± 174 pmol · h⁻¹ · l⁻¹; P < 0.001; Fig. 4B).

Plasma glucagon concentrations were equivalent during baseline (Table 1) and did not increase with hypoglycemia. Unlike the response of plasma epinephrine, plasma glucagon was not influenced by the infusion of fructose. Plasma norepinephrine, growth hormone, and cortisol levels increased with hypoglycemia, but the increments were similar in both sets of studies (Table 1) and unaffected by coinfusion of fructose.

**Glucose kinetics.** [3-3H]glucose specific activity was effectively maintained in both sets of studies during the clamps (Fig. 5). Mean fasting glucose production was similar in the two studies (7.8 ± 1.2 μmol · kg⁻¹ · min⁻¹ for fructose studies and 7.5 ± 1.2 μmol · kg⁻¹ · min⁻¹ for control; NS). During the 5.0- and 4.4-mmol/l glucose steps (after the increase in insulin infusion), EGP was equally suppressed by ~49% in both studies. During the next two clamp steps (3.9 and 3.3 mmol/l), EGP rose to 88 and 98%, respectively, of basal in the fructose studies and to 55 and 54%, respectively, in the control studies (P < 0.001 for both; Fig. 6), consistent with a significantly greater increase of EGP in the fructose studies.

Glucose disposal rates were similar before insulin infusion in all studies. With the initiation of the clamp, glucose disposal rates increased equally in the fructose and control studies by ~1% (to 16.4 ± 2.2 and 15.7 ± 1.9 μmol · kg⁻¹ · min⁻¹, respectively; NS). Consequently, during the 3.9- and 3.3-mmol/l glucose steps, glucose disposal rates de-

### Table 1

<table>
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<th>Fructose</th>
<th>Control</th>
<th>Baseline</th>
<th>Peak</th>
<th>Baseline</th>
<th>Peak</th>
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</thead>
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<tr>
<td>Epinephrine (pmol/l)</td>
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<td>3210 ± 284*</td>
<td>622 ± 74</td>
<td>1999 ± 156</td>
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<td>Norepinephrine (nmol/l)</td>
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<td>2.04 ± 0.38</td>
<td>1.42 ± 0.22</td>
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<td>Cortisol (nmol/l)</td>
<td>223 ± 70</td>
<td>358 ± 50</td>
<td>277 ± 59</td>
<td>372 ± 58</td>
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<tr>
<td>Growth hormone (μg/l)</td>
<td>0.42 ± 0.11</td>
<td>9.16 ± 3.0</td>
<td>0.37 ± 0.49</td>
<td>10.8 ± 6.3</td>
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<tr>
<td>Glucagon (ng/l)</td>
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<td>48.3 ± 6.8</td>
<td>59.3 ± 7.6</td>
<td>55.0 ± 8.51</td>
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Data are means ± SE. *P < 0.05 vs. control.

**FIG. 4.** Plasma epinephrine concentrations over time (A) and averaged for the epinephrine AUC (B). Studies with (fructose; ■) or without (control; ○) coinfusion of fructose. *P < 0.001 vs. control.

**FIG. 5.** Plasma [3-3H]glucose specific activity in the stepped hypoglycemia studies at baseline and averaged for the final 30 min of each glucose step. Studies with (fructose; ■) or without (control; ○) coinfusion of fructose.
were higher during fructose infusion. At this step, despite the fact that plasma glucose levels consistent with the greater increase in plasma epinephrine (3.3-mmol/l glucose step; Fig. 7). This latter observation is consistent with the greater increase in plasma epinephrine at this step, despite the fact that plasma glucose levels were higher during fructose infusion.

DISCUSSION

Our study demonstrates that in type 1 diabetic patients with impaired counterregulation, fructose infused intravenously in a dose catalytic for glucokinase activation induces a dramatic potentiation of the counterregulatory response, characterized by augmentation of the epinephrine response and a significant enhancement of EGP during hypoglycemia. These observations are consistent with similar effects that we observed in nondiabetic individuals (21), suggesting that glucokinase-mediated glucose sensing is involved in some of the defective counterregulatory responses seen with hypoglycemia-associated autonomic failure (HAAF) (rev. in 1).

It should be noted that during infusion of fructose, we observed a significant improvement in the impaired epinephrine response that characterizes patients with type 1 diabetes. Specifically, the epinephrine response to hypoglycemia demonstrated a shift in its glycemic threshold (a significant release of the hormone occurred at a higher plasma glucose concentration) and a higher magnitude of epinephrine release (reflected by both peak and AUC concentrations) compared with control studies. As typical of previously published data in similar type 1 diabetic individuals, epinephrine secretion demonstrated by these individuals in the control studies (both glycemic threshold and magnitude of secretion) was abnormal, with a higher threshold (i.e., a greater stimulus was required to elicit the response) and a decreased maximal response (1,3,21).

Thus, acute fructose infusion seems to normalize epinephrine release during hypoglycemia, with a glycemic threshold and AUC for epinephrine comparable to those seen in nondiabetic healthy individuals (21). Indeed, the epinephrine plasma concentrations during fructose infusion may have been underestimated because the plasma glucose level achieved at the final step was higher than in control studies. In contrast, glucagon secretion was absent in both sets of studies and was unresponsive to fructose infusion, suggesting that the defect in glucagon release during hypoglycemia in type 1 diabetes may represent an unrelated intrinsic abnormality in glucagon release and/or may be dependent on a different mechanism for physiological activation that is altered in type 1 diabetics. Finally, the secretion patterns of other counterregulatory hormones—norepinephrine, cortisol, and growth hormone—increased comparably during hypoglycemia and did not differ significantly between the fructose and control studies, indicating that the fructose-induced effect observed for epinephrine activation was specific. These latter hormones were similarly uninfluenced by fructose in our previous study in nondiabetic individuals (21).

In concert with the augmentation of epinephrine release during hypoglycemia, the fructose studies were accompanied by significantly higher rates of EGP during the 3.9- and 3.3-mmol/l glucose steps and corresponding decreases in glucose infusion rates. Moreover, because of this enhanced counterregulatory response in the fructose studies, we were unable to lower the plasma glucose levels below 3.9 mmol/l. Thus, despite the same plasma insulin concentrations (−205 pmol/l in both studies), we could not attain the final glucose step (3.3 mmol/l target plasma glucose) in the fructose infusion studies, a factor that contributes to underestimation of the magnitude of the counterregulatory response in these studies but emphasizes the potency of the enhanced glucose counterregulation by EGP in preventing further hypoglycemia. In these experiments, a relatively low “physiological” insulin infusion rate was used deliberately to prevent complete (and possibly irreversible) suppression of EGP. A higher insulin infusion rate may have resulted in a more potent counterregulatory response in the fructose studies by achieving the final clamp steps; however, the distal effects of hypoglycemia counterregulation (hormonal and possibly non-hormonal) on EGP would have been masked by insulin-induced suppression of EGP.

It should be noted that fructose per se is a substrate for gluconeogenesis and, hence, could have contributed to the increase in EGP in the fructose studies. However, various
studies have demonstrated that low-dose fructose infusions during euglycemia and hyperglycemia are not associated with increases in EGP (25,30). Similar fructose infusion rates as used in our experiments induced a suppression of EGP during hyperglycemia in patients with type 2 diabetes (24). Furthermore, in previous experiments in nondiabetic individuals, we specifically examined whether fructose infusion could directly influence the rates of EGP or glucose uptake (21). Using the pancreatic clamp technique to suppress glucagon secretion, plasma glucose was lowered to 4.2 mmol/l, and simultaneously an infusion of either fructose (1.2 mg · kg⁻¹ · min⁻¹) or saline was infused. These studies demonstrated no difference in EGP between fructose and control (saline) infusions. However, because neither of these studies used labeled fructose to determine the fraction of fructose metabolized into glucose, we cannot exclude the possibility that in the present studies, fructose was a precursor for gluconeogenesis and or EGP. Nevertheless, owing to a possible increase in hepatic glycogen synthesis during euglycemia (25), fructose infusion may have favored activation of EGP during counterregulation of hypoglycemia, independent of an enhancement of hypoglycemia sensing.

Because glucose homeostasis is normally maintained within a very narrow range, the existence of glucose sensors located in various organs—especially in brain—has been logically deduced. Such brain sensors trigger—via the autonomic nervous system—compensatory changes in glucose utilization and EGP either directly or indirectly through the control of hormonal secretion (31). The existence of neurons that are responsive to glucose has been confirmed by elegant electrophysiologic studies (32). These studies show that the firing rate of some hypothalamic neurons is altered by changes either in plasma glucose or in local extracellular fluid glucose concentrations. Two classes of neurons have been defined: those with increased activity when plasma glucose increases (“glucose-responsive neurons”) and those that decrease their activity under the same conditions (“glucose-sensitive neurons”) (12,32). In support of this paradigm, animal studies have demonstrated activation or inhibition of the counterregulatory response by perfusion of certain areas of the brain with 2-deoxyglucose or glucose, respectively (17,33–35). It is interesting that the same brain areas (the hypothalamus, the substantia nigra of the midbrain, the nucleus of the solitary tract, and motor nucleus of the vagus in the pons) express GLUT 2, glucokinase, GKRP, and KATP Channels, all of which have been implicated in glucose sensing (16,18,32).

The mechanism by which fructose infusion might augment the counterregulatory response to hypoglycemia is not known. In vitro studies have shown that F1P can activate glucokinase translocation by binding to GKRP. GKRP, in turn, inhibits glucokinase in an allosteric manner that is competitive with respect to glucose. Conversely, F6P binds to GKRP and greatly enhances its binding to and inhibition of glucokinase. Thus, fructose infusion can result in two diametrically opposed effects on glucokinase activity, according to the sensing cell type (36–38), and thus may be able to act as a “sensor” for both hyperglycemia or hypoglycemia. Previous in vivo studies have demonstrated that fructose (infused in a similar dose) can modulate hepatic glucose fluxes. Specifically, these studies demonstrated that fructose restores the inhibition of EGP by hyperglycemia and improves oral glucose tolerance in humans with type 2 diabetes, possibly via stimulation of hepatic glucose uptake activating glucokinase (24,39). The possibility that fructose may act similarly at the level of glucose sensing cells localized in the central nervous system is further supported by the recent finding of functional GKRP in the brain (40).

Our previous study in nondiabetic individuals demonstrated that fructose infusion induced an amplification of the counterregulatory response to hypoglycemia characterized by augmentation of epinephrine and glucagon responses and a greater increment in EGP than reflected by the amplified hormonal increments (21). Thus, we hypothesized that fructose action occurred at the level of glucose sensing or at a more proximal integration center. In the current study, hypoglycemia counterregulation was similarly amplified in patients who have type 1 diabetes and lack the glucagon response, suggesting that aminergic activation could have represented its main mechanism of action. Inability of fructose to augment glucagon secretion in these studies does not necessarily invalidate the notion that fructose acts at a central integrated “sensor” site, because there is ample evidence that glucagon secretion during hypoglycemia is regulated by both central and independent local (islet) mechanisms (41–43). It should be noted that the responses of other major counterregulatory hormones—corticosterone, growth hormone, and norepinephrine—are not affected by fructose coinfusion in nondiabetic individuals (21) or in these patients with type 1 diabetes, clearly indicating the complexity and redundancy of hypoglycemic sensing mechanisms.

That the activation of EGP with fructose was disproportionately greater than its effect on epinephrine release suggests that fructose may have additional and possibly independent effects on EGP during hypoglycemia. In support of this possibility, Petersen et al. (30) demonstrated that infusion of a low dose of fructose to nondiabetic individuals during a hyperinsulinemic-euglycemia clamp induces a threefold increase in net hepatic glycogen synthesis. Because net hepatic glycogen synthesis has been shown to be diminished in patients with poorly controlled type 1 diabetes (44), previous activation of glucogen synthesis and increasing net hepatic glycogen content with fructose infusion could possibly contribute to EGP during subsequent hypoglycemia. Alternatively, a greater autonomic drive to counterregulation (with plasma epinephrine as one component) may underlie the dramatic effect of fructose on EGP during hypoglycemia. Finally, it should be noted that fructose infusion was also associated with an exaggerated decrease in glucose uptake, a counterregulatory effect that is likely explained by higher plasma epinephrine concentrations (45).

In conclusion, this study demonstrates that the epinephrine and EGP counterregulatory responses to hypoglycemia in type 1 diabetic patients with impaired glucose counterregulation can be enhanced or restored to the levels seen in nondiabetic individuals with fructose infusion. The augmentation of the counterregulatory response was characterized by a shift in the glycemic threshold for epinephrine (which occurred at a higher plasma glucose
level) and an increase in the magnitude of its secretion. In parallel, a significant activation of EGP and reduction in glucose uptake resulted in prompt recovery from hypoglycemia. Augmenting the counterregulatory response to hypoglycemia could have major implications in the management of patients with type 1 diabetes in whom intensive insulin treatment, although advantageous, is associated with a higher risk for developing impaired counterregulation, HAAF, and severe hypoglycemia. Furthermore, we may speculate that fructose-induced activation of glucokinase either bypasses or corrects the defective metabolic signaling by hypoglycemia in individuals with HAAF, yielding clues to its pathogenesis and/or treatment.

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