Effects of β-adrenergic blockade on hepatic and renal glucose production during hypoglycemia in conscious dogs

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Cersosimo, Eugenio, Irina N. Zaitseva, and Mohamed Ajmal. Effects of β-adrenergic blockade on hepatic and renal glucose production during hypoglycemia in conscious dogs. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E792–E797, 1998.—To investigate the role of β-adrenergic mechanisms in the counterregulatory response of the liver and kidney to hypoglycemia, we studied 10 dogs before and after a 2-h constant infusion of insulin (4 mU·kg⁻¹·min⁻¹) either without (n = 4) or with (8 µg/min, n = 6) propranolol and variable dextrose to maintain hypoglycemia, 7 days after surgical placement of sampling catheters in left renal and hepatic veins and femoral artery. Systemic glucose appearance (Ra) and endogenous (EGP), hepatic (HGP), and renal (RGP) glucose production were measured by a combination of arteriovenous difference and peripheral infusion of [6-3H]glucose, renal blood flow with a flow probe, and hepatic plasma flow by indocyanine green clearance. Without β-adrenergic blockade, arterial glucose decreased from 5.12 ± 0.02 to 2.53 ± 0.07 mmol/l, glucose Ra increased from 17.8 ± 0.7 to 30.5 ± 2.5 (P < 0.01) when EGP was 22.2 ± 0.5, HGP from 13.5 ± 1.1 to 19.3 ± 1.3, and RGP from 2.4 ± 1.0 to 8.6 ± 0.9 µmol·kg⁻¹·min⁻¹ (all P < 0.05). When propranolol was infused, glucose decreased from 5.97 ± 0.02 to 2.71 ± 0.03 mmol/l, glucose Ra increased from 16.3 ± 1.0 to 25.1 ± 1.6 when EGP was 9.9 ± 0.4, HGP decreased from 14.4 ± 0.7 to 10.4 ± 0.6, and RGP decreased from 3.8 ± 1.3 to 1.1 ± 0.8 µmol·kg⁻¹·min⁻¹ (all P < 0.05). Our data indicate that β-adrenergic blockade impairs glucose recovery during sustained hypoglycemia, in part, by preventing the simultaneous compensatory increase in HGP and RGP.

METHODS

Animals and surgery. All studies were approved by the Institutional Animal Care and Use Committee at the State University of New York at Stony Brook and followed National Institutes of Health guidelines for animal experimentation. Seven days before the experiment, a laparotomy was performed in 20- to 25-kg male mongrel dogs (n = 10) under halothane anesthesia, and Silastic sampling catheters were placed in the left renal and hepatic veins and in the aorta, and a flow probe was placed around the left renal artery, as previously described (2).

Experimental protocol. On the morning of the experiment, after an 18-h overnight fast, the catheters and the flow probe were exteriorized under local anesthesia, and an infusion catheter was inserted into the precava via a lateral saphenous vein. The Doppler flow probe was connected to a transducer, and unilateral renal blood flow was monitored continuously throughout the experiment. At 0800 (time = −120 min), after obtaining blood for assay blanks, a primed constant systemic infusion of [6-3H]glucose (10 µCi, 0.20 µCi/min) together with a constant indocyanine green (ICG) infusion (0.08 mg/min) were started and continued to the end of the study. Baseline femoral artery and renal and hepatic vein blood samples were obtained every 10 min from –30 to 0 min for the measurement of microhemocrit, hepatic plasma flow, plasma insulin, glucagon, catecholamines, glucose concentration, and specific activity (SA). After completion of baseline collections, animals were randomized to receive a 2-h constant systemic infusion of either insulin (4 mU·kg⁻¹·min⁻¹) alone (n = 4) or in combination with propranolol (8 µg/min, n = 6) together with a variable infusion of dextrose to maintain hypoglycemia at 2.2 mmol/l. Blood samples were obtained again at 10-min intervals between 90 and 120 min, and, at the end of the experiment, the dog was euthanized with an intravenous infusion of a solution of pentothal and concentrated potassium chloride, and the position of the catheters was verified at necropsy.

Analytic techniques. Plasma glucose concentrations were measured by a glucose oxidase method using a Beckman Glucose Analyzer II (Beckman, Fullerton, CA). Plasma [3H]glucose SA was determined in deproteinized plasma (25) after deionization with ion exchange resins, as previously described (3). Plasma ICG concentration was determined by a colorimetric assay (17); insulin (15) and glucagon (1) by radioimmunoassay; and catecholamines by HPLC (19).

EPINEPHRINE is a potent stimulus for glucose production, and its release plays an important role in glucose recovery during insulin-induced hypoglycemia (11, 16). Evidence suggests that the plasma glucose-raising effect of epinephrine is mediated via both α- and β-adrenergic mechanisms and involves direct and indirect actions, which include stimulation of glucose production and limitation of glucose utilization (8, 22, 23). Epinephrine action to increase hepatic glucose production is largely mediated through β₂-adrenergic receptors and is well documented in dogs (18, 26). The potential contribution of the kidney and the effects of epinephrine on renal glucose production during hypoglycemia, however, are not known. Recent findings indicating that epinephrine infusion increases renal glucose production in postabsorptive healthy subjects (27) and that renal contribution to glucose production in hypoglycemic dogs is enhanced and dependent on elevation of circulating counterregulatory hormones (4) suggest that adrenergic stimulation of glucose production by the kidney may represent an important additional mechanism in the body’s defense against insulin-induced hypoglycemia. The present studies were therefore undertaken to investigate the contribution of the liver and kidney to glucose production during sustained hypoglycemia with simultaneous β-adrenergic blockade in conscious dogs.

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Calculations. Hepatic plasma flow (HPF) was calculated by 
ICG clearance using the following equation
\[
\text{HPF} = \frac{\text{INF}_{\text{ICG}}}{[\text{ICG}]_{\text{a}}} - [\text{ICG}]_{\text{v}}
\]
where INF\(_{\text{ICG}}\) is ICG infusion rate (mg/min), [ICG\(_{\text{a}}\)] is plasma ICG concentration (mg/ml), the subscript a indicates artery, and the subscript v indicates hepatic vein. Left renal plasma flow (RPF) was calculated by multiplying renal blood flow by the 1 – hematocrit factor. Systemic glucose rates of appearance (glucose R\(_{s}\)) were calculated using the steady-state formula
\[
glucose R_{s} = \frac{\text{INF}_{\text{Glc}}}{[\text{Glc}]_{a}} - \left[\frac{[\text{Glc}]_{v}}{[\text{Glc}]_{a}}\right]
\]
where INF\(_{\text{Glc}}\) is the [\(\text{6-}^{3}\text{H}\)glucose infusion rate (dpm/min), and Glc is glucose. Left renal fractional extraction of glucose and splanchnic fractional extraction of glucose (FE\(_{\text{Glc}}\)) were calculated using the following formula
\[
\text{FE}_{\text{Glc}} = \left[\frac{[\text{Glc}]_{a} \times \text{SA}_{a} - [\text{Glc}]_{v} \times \text{SA}_{v}}{[\text{Glc}]_{a} \times \text{SA}_{a}}\right]
\]
where [Glc] is plasma glucose concentration, SA refers to tritiated glucose specific activity, and the subscript v indicates renal or hepatic vein. The numerator in this formula represents \([\text{3H}]\)glucose radioactivity extracted by the kidney or splanchnic tissues, and the denominator represents arterial \([\text{3H}]\)glucose radioactivity. Left renal glucose utilization and splanchnic glucose utilization (utilization) were calculated using the following formula
\[
\text{utilization} = \frac{\text{FE}_{\text{Glc}} \times [\text{Glc}]_{a} \times \text{R(H)PF}}{1}
\]
where R(H)PF equals either unilateral renal plasma flow or hepatic plasma flow. Net left renal glucose balance and splanchnic glucose balance (balance) were calculated using the following formula
\[
\text{balance} = \left[\frac{[\text{Glc}]_{v} - [\text{Glc}]_{a}}{[\text{Glc}]_{a}}\right] \times \text{R(H)PF}
\]
Positive values represent net output and negative values net uptake of glucose. Left renal glucose production and hepatic glucose production (production) were calculated as the algebraic difference between glucose utilization (Eq. 4) and balance (Eq. 5). Because glucose is extracted into whole blood and there is rapid equilibration between red blood cell and plasma glucose concentration, Eqs. 3–5 will underestimate hepatic and renal glucose production and utilization.

Statistics. All values are expressed as means ± SE. Data obtained at baseline in each group were compared with those from the study period using a paired t-test; data between groups during the study periods were compared using a nonpaired t-test. All P values below 0.05 were considered statistically significant.

RESULTS

Unilateral renal plasma flow was 7.45 ± 1.20 and 6.18 ± 1.00 ml·kg\(^{-1}\)·min\(^{-1}\) in the baseline period and did not change significantly [P = not significant (NS)] during hypoglycemia with (7.08 ± 0.70 ml·kg\(^{-1}\)·min\(^{-1}\)) or without (7.83 ± 0.70 ml·kg\(^{-1}\)·min\(^{-1}\)) simultaneous propranolol infusion (P = NS). Hepatic plasma flow increased from 28.20 ± 2.20 to 38.10 ± 2.00 ml·kg\(^{-1}\)·min\(^{-1}\) (P < 0.05) during hypoglycemia, but it did not change (20.46 ± 2.10 vs. 22.97 ± 1.90 ml·kg\(^{-1}\)·min\(^{-1}\), P = NS) when propranolol was infused. Arterial plasma insulin levels increased from 50 ± 4 to 981 ± 67 and from 40 ± 4 to 1,075 ± 75 pmol/l (all P < 0.01) in the hypoglycemia and β-blockade groups, respectively. Table 1 summarizes data on arterial, renal, and hepatic vein plasma glucose concentration and SA in the baseline and during the last 30 min of the hypoglycemic study period with or without β-adrenergic blockade. Net left renal glucose balance switched from −0.74 ± 0.51 to a net output of 1.72 ± 0.40 µmol·kg\(^{-1}\)·min\(^{-1}\) (P < 0.05), and net splanchnic glucose output increased from 12.97 ± 1.27 to 17.91 ± 1.50 µmol·kg\(^{-1}\)·min\(^{-1}\) (P < 0.05) during hypoglycemia. When propranolol was infused, net left renal glucose uptake increased from −1.42 ± 0.61 to −2.69 ± 0.42 µmol·kg\(^{-1}\)·min\(^{-1}\) (P < 0.05 vs. baseline and hypoglycemia without propranolol), and net splanchnic glucose output decreased from 11.46 ± 1.45 to 7.81 ± 0.80 µmol·kg\(^{-1}\)·min\(^{-1}\) (P < 0.05 vs. baseline and hypoglycemia without propranolol). Figure 1 depicts net splanchnic and total renal glucose balance in the baseline and during the last 30 min of the hypoglycemic study period with or without β-adrenergic blockade. Arterial [\(\text{3H}\)]glucose SA was constant during the baseline period and in the last 30 min of the hypoglycemic study period in both groups, indicating steady state had been achieved. Mean plasma [\(\text{3H}\)]glucose SA was consistently lower in the renal and hepatic vein than in the artery in all animals, except that when propranolol was infused in the hypoglycemic period, mean plasma [\(\text{3H}\)]glucose specific activities in the artery and in the renal vein (2,846 ± 231 vs. 2,749 ± 146, P = NS) were not different from each other (Table 1).

Systemic glucose R\(_{s}\) increased from 17.8 ± 0.7 to 30.5 ± 1.5 during hypoglycemia, when endogenous glucose production was 22.2 ± 1.5 µmol·kg\(^{-1}\)·min\(^{-1}\) (P < 0.05 vs. baseline), and from 16.3 ± 1.0 to 25.1 ± 1.6 during hypoglycemia with β-blockade, when endogenous glucose production was 9.9 ± 0.4 µmol·kg\(^{-1}\)·min\(^{-1}\) (P < 0.05 vs. baseline and hypoglycemia without propranolol). During hypoglycemia without β-blockade, renal glucose extraction of glucose increased from 6.2 ± 0.8 to 13.1 ± 0.3% (P < 0.05), renal glucose utilization did not change (1.95 ± 0.48 vs. 2.59 ± 0.37 µmol·kg\(^{-1}\)·min\(^{-1}\), P = NS), and renal glucose produc-

Table 1. Arterial, renal, and hepatic vein plasma Glc concentration and SA in postabsorptive conscious dogs during the baseline period and in the last 30 min of a 120-min hypoglycemic hyperinsulinemic clamp with and without β-adrenergic blockade

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Hypoglycemia</th>
<th>Baseline</th>
<th>β-Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artery Glc</td>
<td>5.12 ± 0.02</td>
<td>2.53 ± 0.07*</td>
<td>5.97 ± 0.02</td>
<td>2.71 ± 0.03*</td>
</tr>
<tr>
<td></td>
<td>4,560 ± 196</td>
<td>2,944 ± 176*</td>
<td>3,939 ± 177</td>
<td>2,846 ± 231*</td>
</tr>
<tr>
<td>Renal vein Glc</td>
<td>5.00 ± 0.04</td>
<td>2.75 ± 0.06†</td>
<td>5.78 ± 0.04</td>
<td>2.33 ± 0.14†</td>
</tr>
<tr>
<td></td>
<td>4,382 ± 149</td>
<td>2,355 ± 107*</td>
<td>3,767 ± 220</td>
<td>2,749 ± 146*</td>
</tr>
<tr>
<td>Hepatic vein Glc</td>
<td>5.58 ± 0.03</td>
<td>3.00 ± 0.04*</td>
<td>6.53 ± 0.06</td>
<td>3.05 ± 0.05*</td>
</tr>
<tr>
<td></td>
<td>4,169 ± 227</td>
<td>2,446 ± 54*</td>
<td>3,514 ± 114</td>
<td>2,425 ± 285*</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE of four values performed in triplicate. Units for glucose (Glc) concentrations are µmol/ml, and units for specific activity (SA) are disintegrations-min\(^{-1}\)·µmol\(^{-1}\). *P < 0.05 vs. baseline. †P < 0.05 vs. baseline and between study groups.
tion increased threefold from 1.21 ± 0.50 to 4.31 ± 0.43 µmol·kg⁻¹·min⁻¹ (P < 0.05). When propranolol was infused during hypoglycemia, renal fractional extraction of glucose increased from 7.4 ± 0.6 to 17.0 ± 0.9% (P < 0.05), renal glucose utilization did not change (3.30 ± 0.70 vs. 3.25 ± 0.35 µmol·kg⁻¹·min⁻¹, P = NS), and renal glucose production decreased from 1.88 ± 0.63 to 0.56 ± 0.42 µmol·kg⁻¹·min⁻¹ (P < 0.05 vs. baseline and hypoglycemia without propranolol). During hypoglycemia without β-blockade, splanchnic fractional extraction of glucose increased from 0.4 ± 0.2 to 1.5 ± 0.4% (P < 0.05), splanchnic glucose utilization did not change (0.52 ± 0.30 vs. 1.42 ± 0.57 µmol·kg⁻¹·min⁻¹, P = NS), and hepatic glucose production increased from 13.49 ± 1.09 to 19.34 ± 1.30 µmol·kg⁻¹·min⁻¹ (P < 0.05). When propranolol was infused during hypoglycemia, splanchnic fractional extraction of glucose increased from 2.4 ± 0.4 to 4.1 ± 0.7% (P < 0.05), splanchnic glucose utilization did not change (2.96 ± 0.60 vs. 2.55 ± 0.56 µmol·kg⁻¹·min⁻¹, P = NS), and hepatic glucose production decreased from 14.42 ± 0.72 to 10.36 ± 0.63 µmol·kg⁻¹·min⁻¹ (P < 0.05 vs. baseline and hypoglycemia without propranolol).

Figure 2 depicts the contribution of the liver and kidney to glucose production in the baseline and during the last 30 min of the hypoglycemic study period with or without β-adrenergic blockade. The sum of hepatic (14.05 ± 0.87) and renal (3.22 ± 1.16) glucose production (17.27 ± 1.86 µmol·kg⁻¹·min⁻¹) is equivalent to endogenous glucose production (glucose Ra = 16.90 ± 1.70 µmol·kg⁻¹·min⁻¹) in postabsorptive dogs (n = 10). In contrast, during hypoglycemia the sum of hepatic (19.34 ± 1.30) and renal (8.62 ± 0.86) glucose production (27.96 ± 2.16 µmol·kg⁻¹·min⁻¹) exceeds endogenous glucose production (22.23 ± 0.48 µmol·kg⁻¹·min⁻¹), as calculated by the difference between systemic glucose Ra (30.48 ± 1.52 µmol·kg⁻¹·min⁻¹) and mean exogenous infusion rates (8.25 ± 0.48 µmol·kg⁻¹·min⁻¹). Similarly, but to a lesser degree, when propranolol is infused, the sum of hepatic (10.36 ± 0.63) and renal (1.12 ± 0.57) glucose production (11.48 ± 1.47 µmol·kg⁻¹·min⁻¹) is slightly higher than endogenous glucose production (9.92 ± 0.48 µmol·kg⁻¹·min⁻¹), as calculated by the difference between systemic glucose Ra (25.12 ± 1.62 µmol·kg⁻¹·min⁻¹) and mean exogenous infusion rates (15.20 ± 0.40 µmol·kg⁻¹·min⁻¹).

In response to hypoglycemia, arterial plasma glucagon and epinephrine levels increased comparably in both groups by 3- and 12-fold, respectively. Arterial plasma norepinephrine levels, however, were higher (P < 0.05) in the presence than in the absence of β-blockade during hypoglycemia (Table 2).

**Table 2.** Arterial plasma glucagon and catecholamine concentrations in postabsorptive conscious dogs during the baseline period and in the last 30 min of a 120-min hypoglycemic hyperinsulinemic clamp with and without β-adrenergic blockade

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Hypoglycemia</th>
<th>Baseline</th>
<th>β-Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucagon</td>
<td>50 ± 3</td>
<td>167 ± 12*</td>
<td>55 ± 5</td>
<td>182 ± 15*</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>130 ± 8</td>
<td>1,825 ± 50*</td>
<td>159 ± 6</td>
<td>1,977 ± 130*</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>129 ± 6</td>
<td>387 ± 15*</td>
<td>246 ± 21</td>
<td>892 ± 65†</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE of four values performed in duplicate. Units are pg/ml. *P < 0.05 vs. baseline. †P < 0.05 vs. baseline and between study groups.

**DISCUSSION**

The present studies confirm previous findings in dogs (3, 4) indicating that renal glucose production, which represents ~15–25% in the postabsorptive state, makes a substantial contribution (up to ~40%) to tracer-determined glucose production during hypoglycemia and further demonstrate that the compensatory elevation in glucose production by the liver and kidney,
which occurs in these hypoglycemic conditions, is prevented by β-adrenergic blockade. Sustained insulin-induced hypoglycemia is associated with a reversal in renal glucose balance to net output, a threefold increase in renal glucose production, and a simultaneous 40% increase in hepatic glucose production. The infusion of propranolol, a nonspecific β-adrenergic blockade, during a comparable degree of hypoglycemia decreases renal glucose production by ~70% and hepatic glucose production by ~30% to values below postabsorptive rates.

As a result, as shown in Fig. 1, β-adrenergic blockade reduces net splanchnic glucose output from 17.91 to 7.81 µmol·kg⁻¹·min⁻¹ and induces a switch from net renal glucose output of 3.44 to net uptake of 5.38 µmol·kg⁻¹·min⁻¹ during hypoglycemia. These observations complement earlier data (4, 9, 13) in support of the view that stimulation of gluconeogenesis, in both the liver and kidney, is critical in sustaining glucose production during hypoglycemia caused by continuous insulin infusion.

Moreover, our findings are consistent with recent reports indicating that hepatic and renal glucose production are enhanced by epinephrine infusion in animals (6, 26) and in humans (27). Although the mechanisms for this increase in gluconeogenesis during insulin-induced hypoglycemia are not entirely clear, in accordance with data published by Frizzell et al. (13) and by Davis et al. (9), our studies provide evidence that the increase in hepatic glucose production during hypoglycemia is largely dependent on an elevation in hepatic plasma flow (from ~28 to ~38 ml·kg⁻¹·min⁻¹ in our series). The fact that this elevation in hepatic plasma flow is entirely avoided by the concomitant infusion of propranolol suggests that β-adrenergic blockade prevents the increment in hepatic glucose production associated with hypoglycemia, in part, by altering blood flow to the liver. The additional possibility that β-adrenergic blockade may reduce hepatic gluconeogenesis during sustained hypoglycemia by decreasing peripheral release and hepatic utilization of gluconeogenic precursors is suggested by the observation that, although hepatic blood flow is maintained, propranolol reduces hepatic glucose production below postabsorptive rates. The latter is further supported by a previous report indicating that peripheral lactate release and hepatic glucose production increase simultaneously during epinephrine infusion (26).

Considering that renal plasma flow is unaffected by hypoglycemia in either the presence or absence of β-adrenergic blockade, our findings implicate that adrenergic stimulation of renal glucose production in hypoglycemia must involve changes in peripheral release and renal utilization of gluconeogenic precursors. Although these were not evaluated in the current studies, recent data obtained in our laboratory demonstrating that increased renal glucose production in hypoglycemic dogs is accompanied by enhanced peripheral release and renal utilization of lactate and glycerol (5) and the fact that propranolol is capable of blocking epinephrine’s inhibition of peripheral glucose utilization and stimulation of adipose tissue lipolysis after insulin-induced hypoglycemia in humans (16) are entirely consistent with the notion that β-adrenergic mechanisms mediate renal gluconeogenesis primarily by an indirect effect on peripheral tissues. Whether β-adrenergic mechanisms alter gluconeogenic efficiency directly in the kidney, as it has been shown in the liver (26), is not known.

The combination of arteriovenous balance and isotope dilution can effectively partition glucose utilization and production in a tissue bed and has been previously applied to investigate splanchnic (12) and renal (3) glucose metabolism. Unlike previous experiments, however, in the present studies glucose production and utilization by the splanchnic tissues and kidney were determined simultaneously. Although estimated rates of glucose Ra and the individual rates of hepatic and renal glucose production in our studies are in close agreement with previously published data in conscious dogs by other investigators (13, 14, 28), the fact that simultaneous measurements across the liver and kidney yield values for endogenous glucose production rates in hypoglycemia that are higher than those determined by conventional steady-state isotope dilution raises interest and concern.

The use of monocompartmental equations can be associated with as much as 20% underestimation of the Ra of glucose under conditions in which there are large and rapid changes in plasma SA, such as during hyperinsulinemia (7,10). Thus, even though isotopic steady state was approximated during the last 30 min of the hypoglycemic periods when statistical comparisons were made in our studies, underestimation of overall glucose Ra may have been partly responsible for these discrepancies. Nonetheless, the possibility that both hepatic and renal glucose production may have been overestimated in these conditions cannot be discarded. The use of arteriovenous difference combined with tracer dilution across a tissue or organ overestimates the rate of release of a tracee into the venous efflux to the extent that the bidirectional movement of a tracer between the two compartments reflects the relative intracellular abundance of a tracee, particularly if isotope equilibrium has not been reached. In addition, it does not take into account possible tracer dilution that might occur in an intermediary compartment, i.e., “ideal precursor pool” (29). These discrepancies underscore the need to interpret data obtained with arteriovenous difference and isotope dilution techniques with caution and suggest that our calculated rates of hepatic and renal glucose production might represent a near-quantitative assessment of true rates. On the other hand, analyzing each individual rate separately, our results demonstrate that, while the contribution of the liver to endogenous glucose production in hypoglycemia increases by ~40%, that of the kidney increases by approximately threefold. Propranolol infusion induces an ~30% reduction in hepatic glucose production and almost completely suppresses renal glucose production, despite sustained hypoglycemia.
The observation that the β-adrenergic blocking agent propranolol impairs the recovery of plasma glucose after insulin-induced hypoglycemia by reducing hepatic and renal glucose production is of potential clinical significance. Varying degrees of blunted epinephrine response and inappropriate rebound in endogenous glucose production have been documented in hypoglycemic healthy subjects (16) and in patients with diabetes (20, 21, 24). Our animal data provide evidence that glucose production by the kidney, in addition to the liver, is blocked by propranolol and could be partly responsible for the delay in glucose recovery during insulin-induced hypoglycemia. This is particularly important, especially in view of the fact that epinephrine appears to play a greater role in glucose counterregulation during prolonged, as opposed to brief, hypoglycemia (11), a condition more likely to occur in insulin-treated diabetes patients. Therefore, it is conceivable that patients using β-blocking agents are prone to hypoglycemia because of defective counterregulation attributed to simultaneous inhibition of hepatic and renal glucose production. Further studies are required to determine whether propranolol is capable of reducing glucose production by the human kidney and whether renal glucose production plays any role in plasma glucose recovery in patients with diabetes under comparable hypoglycemic conditions.

In summary, we have confirmed that glucose production by the liver and kidney increases concomitantly during insulin-induced hypoglycemia in conscious dogs. Propranolol significantly reduces both hepatic and renal glucose production, which may impair the glucose counterregulatory response to prolonged hypoglycemia. Although the mechanisms are not entirely clear, our data indicate that the compensatory increase in glucose production by the liver is largely dependent on a rise in hepatic plasma flow, which is entirely blunted by β-blockade. In contrast, renal plasma flow is unaffected, thus suggesting that propranolol may also decrease peripheral release and renal utilization of gluconeogenic precursors. We conclude that β-adrenergic blockade impairs glucose recovery during sustained hypoglycemia, in part, by preventing the simultaneous compensatory increase in hepatic and renal glucose production.

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