The Adrenergic Contribution to Glucose Counterregulation in Type I Diabetes Mellitus

Dependency on A-Cell Function and Mediation Through Beta$_2$-Adrenergic Receptors

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SUMMARY

In order to assess the adrenergic contribution to hypoglycemic glucose counterregulation in type I diabetes mellitus and to determine whether the adrenergic contribution is mediated through beta$_1$- or beta$_2$-adrenergic receptors, hypoglycemia was induced by an i.v. insulin infusion (30 mU/m^2 · min) for 60 min in 11 insulin-dependent diabetic patients (IDDM), 5 with normal plasma glucagon responses and 6 with blunted responses, and also in 7 age–weight-matched nondiabetic subjects. Rates of plasma glucose decrease and postnadir increase, as well as plasma concentrations of free insulin and of counterregulatory hormones, were measured when insulin was infused alone, and when insulin was infused along with propranolol (a beta$_1$- and beta$_2$-adrenergic receptor antagonist) or metoprolol (a selective beta$_1$-antagonist). Postnadir plasma glucose recovery was decreased in IDDM with blunted plasma glucagon responses (21 ± 0.8 μmol · L^{-1} · min^{-1}, P < 0.001), but was normal in patients with normal plasma glucagon responses (30 ± 0.4 versus 33 ± 0.5 μmol · L^{-1} · min^{-1} in nondiabetic subjects, P = NS). Postnadir plasma glucose recovery was not affected by either propranolol or metoprolol in normal subjects and in IDDM with normal glucagon responses. However, in IDDM with blunted plasma glucagon responses, postnadir plasma glucose recovery was further decreased by propranolol (14 ± 0.6 μmol · L^{-1} · min^{-1}, P < 0.01), but was unaffected by metoprolol (22 ± 0.9 μmol · L^{-1} · min^{-1}, P = NS).

These results demonstrate that, as in normal man, adrenergic mechanisms are not essential for normal plasma glucose recovery from hypoglycemia in IDDM with normal plasma glucagon responses. However, in IDDM with blunted plasma glucagon responses, adrenergic mechanisms become important for glucose counterregulation although they do not fully compensate for the blunted plasma glucagon responses. Since propranolol delayed plasma glucose recovery from hypoglycemia in IDDM with blunted glucagon responses but metoprolol had no effect, the adrenergic contribution to glucose counterregulation appears to be mediated through beta$_2$-adrenergic receptors. DIABETES 32:887–893, October 1983.

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It has been suggested that in man an appropriate increase in glucagon secretion is essential for prompt restoration of normoglycemia after insulin-induced hypoglycemia and that adrenergic mechanisms become more important only when glucagon secretion is impaired.[1] This suggestion is supported by studies in which an inverse correlation has been found between plasma glucose recovery during beta-adrenergic blockade and residual A-cell function in insulin-dependent diabetic patients,[2,3] who represent a natural model of blunted release of glucagon during hypoglycemia.[2–15] However, the degree to which counterregulation in insulin-dependent diabetic patients is dependent on adrenergic mechanisms is unclear since, although most studies indicate that plasma glucagon responses to hypoglycemia are blunted in type I diabetes mellitus,[2–15] it has been shown recently that this is not always the case:[16] normal plasma glucagon responses to moderate hypoglycemia occur in patients with recent onset of type I diabetes mellitus and the responses progressively decrease with increasing duration of diabetes.[16,17] This heterogeneity of A-cell responses to hypoglycemia raises the question whether counterregulation in diabetic patients with normal or nearly normal plasma glucagon responses is dependent upon adrenergic mechanisms as it is in patients with impaired A-cell responses.

The aim of this study was to determine the extent to which the adrenergic mechanisms contribute to hypoglycemic glucose counterregulation in type I diabetes mellitus with and without impaired A-cell responses to hypoglycemia. In addition, in view of the important role of catecholamines in defense against hypoglycemia in diabetic patients with impaired plasma glucagon responses, which appear to be mediated through beta-receptors,[3] we attempted to establish whether these adrenergic effects were mediated through $beta_1$- or $beta_2$-mechanisms.

MATERIALS AND METHODS

SUBJECTS

Seven nondiabetic healthy subjects within 10% of their ideal body weight and 11 insulin-dependent diabetic patients matched for age and body weight were studied after obtaining fully informed consent (Table 1). Apart from diabetes, the diabetic patients had no other illnesses and were taking no medications other than insulin. The diabetic patients were divided into two groups based on their plasma glucagon response to moderate insulin-induced hypoglycemia in a recent series of studies.[3,16] Group I consisted of five diabetic patients with normal plasma glucagon responses to hypoglycemia, while group II consisted of six patients with more than a 50% reduction in plasma glucagon responses (Table 1).

Other than their A-cell responses to hypoglycemia, group I patients differed from group II patients only in having a shorter duration of diabetes. There was no difference in their plasma C-peptide response to an i.v. injection of 1 mg glucagon, mean 24-h plasma glucose concentration over the 3 days preceding each study, circulating ketoamine HbA_1, and insulin-binding capacity of serum.

Three subjects in group II (nos. 7, 8, and 11) had background retinopathy. In all patients endogenous creatinine clearance was above 90 ml/min. Optimization of blood glucose control was attempted in all diabetic patients for at least 3 days before the initiation of the studies by administering insulin as three daily s.c. injections, i.e., regular insulin before breakfast and before lunch (Actrapid MC U-40, Novo Industries, Copenhagen, Denmark) and a mixture of regular and lente insulins (Novo) before dinner.

PROTOCOLS

Insulin hypoglycemia (saline study). All diabetic and nondiabetic subjects were studied after an overnight fast in the supine position. In the diabetic subjects long-acting insulin was discontinued at least 48 h before the study and four injections of regular insulin were administered daily. On the day before the study, the patients received regular insulin at breakfast, lunch, and dinner; 2–3 h after dinner, two 19-gauge butterfly needles were inserted in two antecubital veins of the same arm and kept patent with 0.9% NaCl infusion (0.5 ml/min).

The proximal venous access was used to infuse regular insulin (Actrapid MC U-40) overnight by means of a syringe pump (model 2681, Harvard Apparatus Co., Inc., Millis, Massachusetts) to maintain blood glucose concentration between 4.5 and 5.5 mmol/L until the beginning of the experiment the next morning. The rate of the overnight insulin infusion was adjusted according to glucose measurements on blood drawn from the distal i.v. line every 5–30 min (Dextrometer, Ames, Miles Laboratories, Elkhart, Indiana). At 9 a.m., a third 19-gauge butterfly needle was inserted in an antecubital vein of the contralateral arm for the intermittent blood sampling. After at least a 45-min equilibration period, baseline blood samples were taken at −15 and 0 min, and at 10–15-min intervals over the next 150 min. In both nondiabetic and diabetic subjects between 0 and 60 min, regular insulin diluted to ≈0.8 U/ml in 0.9% NaCl (to which 1 ml of the subject's blood per 25 ml infusate was added) was infused at the rate of 30 $mU/m^2 \cdot min$. In the diabetic patients this was superimposed on the basal insulin infusion rate required to maintain euglycemia from −60 to 0 min; 50% of the basal insulin infusion rate was used from 60 throughout 150 min.

Effects of nonselective (propranolol) and selective (metoprolol) beta-adrenergic blockade. All nondiabetic and diabetic subjects underwent two additional studies over a 4–6-day interval; either propranolol, a nonselective beta-adrenergic antagonist (Imperial Chemical Industries, S.p.A., Milano) or metoprolol, a highly selective $beta_1$-adrenergic antagonist (Ciba-Geigy, S.p.A., Milano), was infused at the rate of 100 μg/min from 0 throughout 150 min after a priming dose of 3 mg at 0 min; the same amount of insulin given in the above study was also infused. The sequence of the propranolol, metoprolol, and control studies was varied at random.

Hemodynamic studies. In order to assess whether propranolol and metoprolol in doses used above had similar $beta_1$-blocking effects the effects of these agents on exercise-induced tachycardia were estimated in all the diabetic and nondiabetic subjects on different occasions from the hypoglycemia studies. With subjects in the postabsorptive state (10–11 a.m.), heart rate (continuous EKG monitoring) was determined after at least 45 min of supine positioning at bed rest and after two 6-min periods of cycle-ergometer exercise separated by 90 min; the ergometer work load was adjusted to give a heart rate of ≈125 beats/min during the control study, and the same load was used during infusion of either propranolol and metoprolol in doses identical to those used in the hypoglycemia studies.

Analytic methods. Blood for plasma glucose was collected in the Na-fluoride tubes and determined by means of a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, California). All blood samples for hormone determinations were centrifuged immediately after each experiment, and the resultant plasma was stored at −20°C until assay. Plasma was extracted with polyethylene glycol for determination of free insulin (henceforth referred to simply as insulin)[18] and C-peptide[19] in both diabetic and in nondiabetic subjects. Plasma glucagon (30 K antiserum), cortisol, growth hormone, epinephrine, norepinephrine, anti-insulin antibodies, and circulating ketoamine HbA_1 were determined as previously described.[16]

Calculations and statistical methods. All data are expressed as mean ± SEM. Paired and, when appropriate, unpaired Student's *t* test was used for evaluation of statistical significance. The rate of plasma glucose recovery was calculated from the time interval between plasma glucose nadir and return to baseline. In the diabetics in whom the postnadir

TABLE 1
Clinical features of the subjects (mean ± SEM)

Subject no.	Age (yr)	Diabetes duration (mo)	Body surface area (m^2)	C-peptide* (ng/ml)	Mean plasma glucose† (mmol/L) Study: Saline	PRP	MTP	Circulating ketoamine HbA_1‡ (%) Study: Saline	PRP	MTP	Plasma glucagon responses to hypoglycemia (refs. 3, 16)§ (ng/ml · 150 min)
Diabetic subjects											
Group I											
1	21	6	1.73	0.11 (0.13)	7.6 ± 0.6	7.5 ± 0.8	7.8 ± 0.5	8.1	8.0	8.0	7.45
2	27	6	1.83	0.08 (0.08)	8.4 ± 0.8	8.2 ± 0.6	8.3 ± 0.8	7.6	7.8	7.8	8.17
3	18	7	1.75	0.13 (0.24)	7.3 ± 0.9	7.4 ± 0.8	7.8 ± 0.7	8.3	8.3	8.2	7.13
4	24	7	1.73	0.07 (0.06)	8.6 ± 0.5	8.3 ± 0.8	7.6 ± 0.7	9.1	9.0	8.9	7.88
5	34	6	1.73	0.06 (0.09)	9.1 ± 0.7	8.7 ± 0.5	8.5 ± 0.9	7.6	7.5	7.7	7.23
Group II											
6	25	66	1.86	0.06 (0.06)	7.8 ± 0.3	7.5 ± 0.6	8.1 ± 0.2	8.4	8.3	8.2	3.44
7	30	124	1.90	0.16 (0.19)	8.5 ± 0.8	9.1 ± 0.9	8.3 ± 0.6	8.1	7.9	7.9	2.67
8	27	192	1.72	0.07 (0.08)	9.3 ± 0.5	8.3 ± 0.7	7.6 ± 0.7	7.8	8.1	7.9	2.38
9	36	68	1.70	0.13 (0.11)	7.8 ± 0.4	7.6 ± 0.6	7.8 ± 0.8	9.3	9.5	9.3	3.88
10	19	19	1.85	0.12 (0.15)	8.3 ± 0.7	8.2 ± 0.6	7.9 ± 0.8	8.3	8.4	8.4	4.20
11	19	150	1.77	0.09 (0.09)	8.0 ± 0.7	8.1 ± 0.7	8.3 ± 0.6	8.7	8.8	8.9	3.33
Normal subjects						Fasting					
N = 7	26 ± 3		1.79 ± 0.1	0.98 ± 0.10 (2.95 ± 0.4)		4.3 ± 0.1			6.19 ± 0.015		7.78 ± 0.4

*Values obtained 6 min after 1 mg glucagon i.v. are shown in parentheses.
†Mean of fasting and three postprandial (90 min) plasma glucose concentrations over the 3-day period before saline, propranolol (PRP), or metoprolol (MTP) studies.
‡Determined on the morning of each study.
§Areas under the 0–150-min curve.

plasma glucose concentration did not reach baseline values within 150 min, the rate of plasma glucose increase to the 150-min value was employed. The heart rate responses to exercise were calculated from the average heart rate determined at 1-min intervals observed during the 6-min exercise period and the subsequent 10-min period.

RESULTS

There was no difference in the insulin infusion rates required to maintain normoglycemia during the 60 min before each study in diabetic patients with normal A-cell responses to hypoglycemia (group I) and those patients with blunted responses (group II) (group I: saline 5.8 ± 0.3 mU/m² · min, propranolol 6.1 ± 0.2 mU/m² · min, metoprolol 6.2 ± 0.2 mU/m² · min, P = NS; group II: saline 6.0 ± 0.2 mU/m² · min, propranolol 6.4 ± 0.2 mU/m² · min, metoprolol 5.8 ± 0.2 mU/m² · min, P = NS).

Insulin hypoglycemia (saline study) (Figure 1). Baseline plasma insulin, glucose, and counterregulatory hormone concentrations and the plasma glucose nadirs after infusion of insulin were not different in nondiabetic subjects and group I and II diabetic patients. The rate of postnadir increase in plasma glucose concentration in diabetic patients of group I was not different from that of nondiabetic subjects (30 ± 0.4 versus 33 ± 0.5 μmol · L⁻¹ · min⁻¹, P = NS), whereas diabetic patients of group II had a slower plasma glucose recovery (21 ± 0.8 μmol · L⁻¹ · min⁻¹, P < 0.001). The plasma concentrations of insulin and counterregulatory hormones in group I diabetic patients and nondiabetic subjects were not significantly different. In diabetic patients of group II, however, the plasma glucagon response was blunted and plasma epinephrine, cortisol, and growth hormone responses were greater than those of group I and of nondiabetic subjects (area under the curve, P < 0.05).

Effect of propranolol (Figure 1). Baseline plasma insulin, glucose, and counterregulatory hormone concentrations were comparable in the saline and propranolol studies (P = NS). Plasma insulin concentrations during and after the insulin infusions were unaffected by propranolol in all groups. The plasma glucose concentrations in group I diabetic and nondiabetic subjects were unaffected by propranolol, whereas in group II diabetics propranolol decreased the plasma glucose nadir (1.88 ± 0.12 versus 2.33 ± 0.1 mmol/L, P < 0.025) and further decreased the rate of postnadir increase (14 ± 0.6 versus 21 ± 0.8 μmol · L⁻¹ · min⁻¹, P < 0.01). During infusion of propranolol, plasma glucagon, norepinephrine, or cortisol responses were unaffected in all three groups (P = NS), but plasma epinephrine and growth

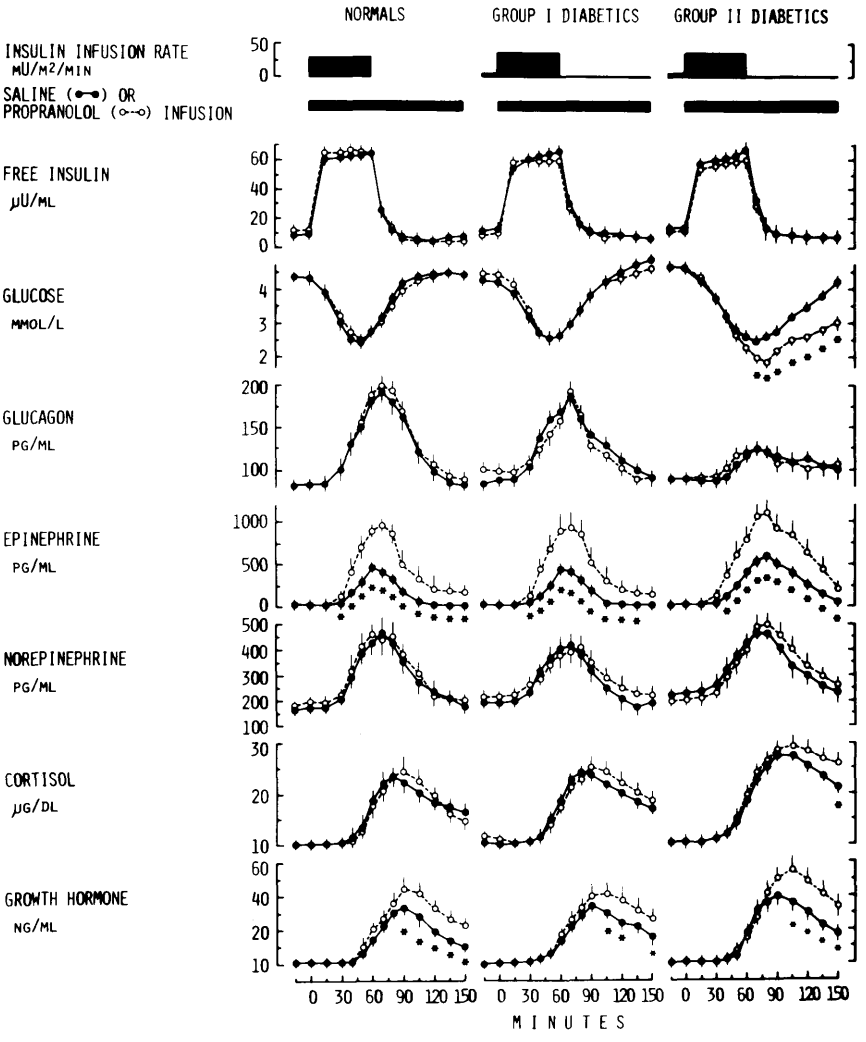

FIGURE 1. Effects of propranolol infusion on plasma concentrations of free insulin, glucose, and counterregulatory hormones in response to an i.v. insulin infusion (30 mU/m² · min) in seven normal subjects, in five insulin-dependent diabetics with normal glucagon responses to hypoglycemia (group I), and in six other diabetics with blunted glucagon responses (group II). *P < 0.05 propranolol versus saline.

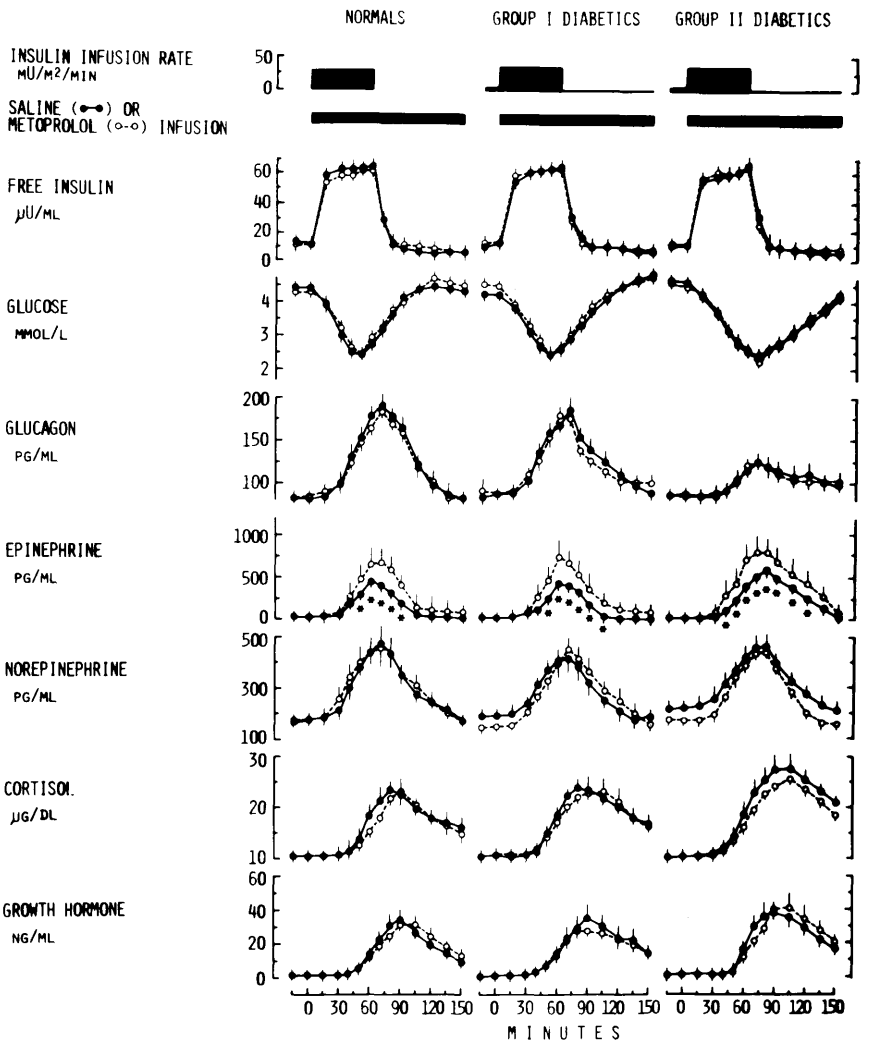

FIGURE 2. Effects of metoprolol on plasma concentrations of free insulin, glucose, and counterregulatory hormones in response to an i.v. insulin infusion (30 mU/m² · min) in seven normal subjects, in five insulin-dependent diabetics with normal glucagon responses to hypoglycemia (group I), and in six other diabetics with blunted glucagon responses (group II). *P < 0.05 metoprolol versus saline.

hormone responses were increased ($P < 0.05$). These increases were similar in all three groups, 2.5–3-fold for epinephrine and 1.5–2-fold for growth hormone.

Effect of metoprolol (Figure 2). Baseline plasma insulin, glucose, and counterregulatory hormone concentrations were not different from those during saline and propranolol studies. Metoprolol had no effect on plasma insulin, glucose, cortisol, growth hormone, and norepinephrine concentrations in all three groups. However, during infusion of metoprolol plasma epinephrine was increased to a greater extent (1.5–2-fold) than during the saline study in all three groups ($P < 0.05$). This increase was less than the increase observed during the infusion of propranolol in all three groups examined ($P < 0.05$).

Effects of propranolol and metoprolol on hemodynamic responses to exercise and hypoglycemia (Tables 2 and 3). Exercise-induced tachycardia (Table 2) and increases in heart rate during hypoglycemia (Table 3) were similarly decreased during infusion of propranolol and metoprolol, consistent with each agent causing a similar degree of $beta_1$-adrenergic blockade. Diastolic blood pressure was lower during metoprolol than during propranolol infusion in the hypoglycemia studies, suggesting that metoprolol had little, if any, $beta_2$-adrenergic antagonistic effects under these conditions.

DISCUSSION

In the present experiments, an intravenous insulin infusion was continued throughout the study in the diabetic patients. Under these conditions, any recovery of plasma glucose from hypoglycemia in the diabetic patients should be due to factors other than the rapid decline of plasma insulin concentrations that occurs after a bolus of intravenous insulin

TABLE 2
Heart rate (beat/min) during rest (30-min bed rest) and during two 6-min exercise periods 30 and 120 min after infusion of saline (0.5 ml/min), propranolol, or metoprolol (3 mg bolus plus 100 μg/min) in the diabetic and nondiabetic subjects (considered together)

	Saline	Propranolol	Metoprolol
Rest	76 ± 5	64 ± 4*	63 ± 3*
Exercise at 30 min	123 ± 5	97 ± 5*	99 ± 5*
Exercise at 120 min	126 ± 6	94 ± 4*	97 ± 4*

*P < 0.01 versus saline.

TABLE 3
Heart rate (beat/min) and blood pressure (mm Hg) before, during, and after i.v. insulin infusion (diabetic and nondiabetic subjects are considered together)

	0 min	60 min	90 min	120 min
Heart rate				
Saline	70 ± 3	81 ± 5*	75 ± 3*	70 ± 2
Propranolol	65 ± 2*	56 ± 2†	56 ± 2†	55 ± 1†
Metoprolol	66 ± 3†	58 ± 2†	56 ± 1	55 ± 1
Systolic blood pressure				
Saline	110 ± 2	116 ± 7	110 ± 4	108 ± 3
Propranolol	110 ± 3	115 ± 4	108 ± 4	105 ± 2
Metoprolol	108 ± 2	114 ± 4	108 ± 3	105 ± 2
Diastolic blood pressure				
Saline	76 ± 2	64 ± 3*	72 ± 2	75 ± 2
Propranolol	77 ± 2	86 ± 4*‡	80 ± 3†	77 ± 2
Metoprolol	77 ± 2	73 ± 4	75 ± 3	75 ± 1

*$P < 0.05$ versus 0 min; †$P < 0.05$ propranolol and metoprolol versus saline; ‡$P < 0.05$ propranolol versus saline and metoprolol.

injection. Potentially, these factors include both hepatic glucose autoregulation[20] and neural and hormonal counterregulatory responses to hypoglycemia; however, only hormonal factors have been proven to be critical for restoration of normoglycemia after hypoglycemia.[21] In the present study there was a prompt restoration of normoglycemia after hypoglycemia and lack of effect of beta-adrenergic blockade in diabetic patients with short-term diabetes who had normal A-cell responses. These observations indicate that adrenergic mechanisms are not critical for restoration of normoglycemia in patients with appropriate A-cell responses to hypoglycemia and that, as in nondiabetic individuals, glucagon is the most important counterregulatory hormone during moderate hypoglycemia.[1,22] Although glucose counterregulation appeared to be normal in patients with recent-onset diabetes, in patients with longer duration of diabetes who had impaired A-cell responses, glucose counterregulation was impaired, despite greater increases in plasma catecholamines. The fact that beta-adrenergic blockade further impaired glucose counterregulation indicates that adrenergic mechanisms play an important counterregulatory role in these glucagon-deficient diabetic subjects. Thus, these studies support the conclusions of Popp et al.[2] and Bolli et al.[3] that patients with insulin-dependent diabetes are dependent upon beta-adrenergic mechanisms to promote recovery of plasma glucose from hypoglycemia in direct proportion to the impairment of A-cell responses. The increased catecholamine response does not seem to fully compensate for impaired A-cell function since restoration of normoglycemia was still delayed. Whether this represents a relative decrease in catecholamine secretory capacity or simply the inability of catecholamines to substitute completely for glucagon remains to be determined.

The present study indicates that the adrenergic contribution to glucose recovery from hypoglycemia in diabetic patients with impaired secretion of glucagon is largely mediated through $beta_2$-adrenergic receptors. This conclusion is based on the observation that plasma glucose recovery during infusion of propranolol (a nonselective beta-adrenergic anatagonist) was diminished, whereas infusion of metoprolol (a highly selective $beta_1$-adrenergic antagonist) had no effect. A similar conclusion was arrived at in a recent study of insulin-induced hypoglycemia in type I diabetic patients employing oral doses of metoprolol and propranolol.[23] However, in that study restoration of euglycemia was not examined. Furthermore, the fact that both the doses of insulin used and the initial plasma glucose concentrations differed in the propranolol and metoprolol experiments, and the fact that plasma glucose concentrations differed by less than 0.5 mmol/L after propranolol and metoprolol make that conclusion somewhat questionable.

In the present study the observation that propranolol but not metoprolol prevented the counterregulatory effects of catecholamines in the diabetics with impaired glucagon responses could be interpreted as being solely the result of the selectivity of metoprolol for $beta_1$-adrenergic receptors. However, it is likely that metoprolol at the dose used also had some effects on $beta_2$-receptors. Plasma epinephrine concentrations increased 1.5–2-fold in response to hypoglycemia during metoprolol infusion. One would thus have expected a greater counterregulatory effect if $beta_2$-receptors were unaffected. However, no enhanced counterregulatory effect was observed. This interpretation of relative rather than absolute selectivity of metoprolol for $beta_2$-receptors is consistent with the demonstration of partial antagonism of metoprolol at doses below those used in the present study on epinephrine-mediated $beta_2$-actions such as broncodilation[24] and vasodilation.[25]

Identical amounts of propranolol and metoprolol were infused in the present study, since it has been recently shown,[26] and confirmed in the present study, that identical doses of the two drugs given i.v. produce similar $beta_1$-blocking effects in terms of reducing exercise-induced tachycardia. Since the ratio between equipotent oral and intravenous doses of metoprolol has been estimated about 2.5[27] and since in the present study 0.1 mg/min of metoprolol was infused, one could consider that the oral dose of metoprolol required to reproduce comparable $beta_1$-blockade to that produced in the present study would be 350–400 mg/day. Considering that the dose of metoprolol usually given orally is less than 400 mg/day, the results obtained in the present study suggest that metoprolol in the usual therapeutic dose would not interfere with plasma glucose recovery from hypoglycemia in glucagon-deficient diabetic subjects.

The plasma concentration of epinephrine in response to hypoglycemia in the present study was increased during the infusion of propranolol, as previously observed.[2,3] This is in agreement with the suggestion that beta-adrenoreceptor

mechanisms play an important role in mediating the removal of epinephrine from plasma.[28] In this regard, the observation that the plasma epinephrine levels in response to hypoglycemia were significantly lower during infusion of metoprolol than during infusion of propranolol in the present study suggests that beta$_2$-adrenoreceptors are involved in the plasma epinephrine clearance. Furthermore, since the growth hormone response to hypoglycemia was enhanced during propranolol but not during metoprolol infusion, the present study also suggests that the adrenergic-mediated inhibition of growth hormone release during hypoglycemia[29] is mediated through beta$_2$-adrenoreceptors.

In conclusion, the present study demonstrates that adrenergic mechanisms are not essential for restoration of normoglycemia from moderate hypoglycemia in diabetic patients with a normal A-cell response, whereas it supports the view that catecholamines are important in patients with blunted response of glucagon. This counterregulatory action of catecholamines appears to be mediated through beta$_2$-adrenergic mechanisms since administration of metoprolol, a highly selective beta$_1$-adrenergic antagonist at doses well above the usual therapeutic range, did not interfere with restoration of normoglycemia, whereas comparable doses of propranolol, a beta$_1$- and beta$_2$-adrenergic antagonist, further impaired plasma glucose recovery from hypoglycemia.

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