Role of Epinephrine-mediated β-Adrenergic Mechanisms in Hypoglycemic Glucose Counterregulation and Posthypoglycemic Hyperglycemia in Insulin-dependent Diabetes Mellitus

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ABSTRACT Initially euglycemic (overnight insulin-infused) patients with insulin-dependent diabetes mellitus (IDDM), compared with nondiabetic controls, exhibit similar, but somewhat delayed plasma glucose nadirs, delayed glucose recovery from hypoglycemia, and posthypoglycemic hyperglycemia after the rapid intravenous injection of 0.075 U/kg of regular insulin. These abnormalities are associated with and potentially attributable to markedly diminished glucagon secretory responses, partially reduced epinephrine secretory responses and delayed clearance of injected insulin in the diabetic patients. Because glucagon normally plays a primary role in hypoglycemic glucose counterregulation and enhanced epinephrine secretion largely compensates for glucagon deficiency, we hypothesized that patients with IDDM, who exhibit diminished glucagon secretory responses to hypoglycemia, would be more dependent upon epinephrine to promote glucose recovery from hypoglycemia than are nondiabetic persons. To test this hypothesis, glucose counterregulation during β-adrenergic blockade with propranolol was compared with that during saline infusion in both nondiabetic controls and in patients with IDDM. Glucose counterregulation was unaffected by β-adrenergic blockade in controls. In contrast, glucose recovery from hypoglycemia was significantly impaired during β-adrenergic blockade in diabetic patients. This finding confirms the hypothesis that such patients are more dependent upon epinephrine-mediated β-adrenergic mechanisms to promote glucose recovery from hypoglycemia and indicates that the measured deficiency of glucagon secretion is functionally important in patients with IDDM. Further, in the time frame of these studies, posthypoglycemic hyperglycemia was prevented by β-adrenergic blockade in these patients. There was considerable heterogeneity among the diabetic patients with respect to the degree to which β-adrenergic blockade limited the posthypoglycemic rise in plasma glucose. This rise was directly related to the degree of residual glucagon secretion and inversely related to plasma-free insulin concentrations.

Thus, we conclude: (*a*) that patients with IDDM are, to varying degrees, dependent upon epinephrine-mediated β-adrenergic mechanisms to promote glucose recovery from hypoglycemia and that the degree of this dependence upon epinephrine is an inverse function of the residual capacity to secrete glucagon in response to hypoglycemia in individual patients; (*b*) that sympathoadrenal activation, coupled with the inability to secrete insulin, plays an important role in the pathogenesis of posthypoglycemic hyperglycemia in patients with IDDM.

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INTRODUCTION

Theoretically, glucose recovery from hypoglycemia could be mediated by hormonal, neural, or autoreg-

ulatory mechanisms or a combination of these. A series of studies in normal human subjects (1–3) recently reviewed (4) indicate that glucagon secretion is normally the primary determinant of glucose recovery from hypoglycemia and that enhanced epinephrine secretion largely compensates for deficient glucagon secretion.

Patients with insulin-dependent diabetes mellitus (IDDM)[1] commonly have blunted glucagon secretory responses to hypoglycemia (5–7) and to nonhypoglycemic plasma glucose decrements (8). Thus, we hypothesized that such patients would be more dependent upon epinephrine-mediated β-adrenergic mechanisms (9) to promote glucose recovery from hypoglycemia than are nondiabetic persons with intact glucagon secretion.

Viberti, Keen, and Bloom (10, 11) recently examined the effects of β-adrenergic antagonists on insulin induced hypoglycemia in diabetic and nondiabetic subjects. In agreement with most previous studies (4), these investigators found little, if any, effect of β-adrenergic blockade on glucose recovery from hypoglycemia in nondiabetic subjects (10). Using an experimental design that included rapid intravenous injection of 6 or 12 U of regular insulin followed by infusion of 6 U insulin/h until the plasma glucose concentration was <36 mg/dl (requiring 30–180 min), they found essentially no glucose recovery from hypoglycemia over 60 min in studies of insulin-treated, initially hyperglycemic patients with diabetes during placebo administration (11). These findings suggest that impaired recovery from hypoglycemia is a function of diabetes per se. This conclusion, however, must be qualified by the fact that their patients with diabetes received substantially larger total insulin doses than did their nondiabetic subjects, which provides a possible explanation for delayed glucose recovery in the former group. Since there was no recovery from hypoglycemia in their placebo group, these investigators were unable to assess any possible effects of β-adrenergic blockade on glucose recovery from hypoglycemia in patients with IDDM. In general, these findings were similar to those of an earlier study by Lager et al. (12). The latter investigators also used variable doses of insulin and observed little glucose recovery from hypoglycemia during control studies in diabetic patients. Postnadir blood glucose concentrations were not significantly reduced by propranolol although it was concluded that the rate of increase in blood glucose was reduced.

We have studied glucose recovery from insulin-induced hypoglycemia, and posthypoglycemic hyperglycemia, in initially euglycemic (overnight insulin-infused) patients with IDDM. This permitted use of the same dose of rapidly injected regular insulin to produce comparable degrees of hypoglycemia in both diabetic patients and controls. The studies were specifically designed to permit comparison of the degree of glucose recovery and posthypoglycemic hyperglycemia during saline infusion with that during β-adrenergic blockade in patients with IDDM and in controls.

METHODS

Subjects. Eight patients with insulin-dependent (type 1) diabetes mellitus (IDDM), whose characteristics are listed in Table I, and seven nondiabetic controls consented to participate. All subjects were within 20% of their ideal body weights (Metropolitan Life Insurance Company tables). The mean (±SE) ages of the patients (28±2 yr) and the controls (24±1 yr) were not significantly different. Similarly, the mean body weights of the patients (67.1±4.1 kg) did not differ from those of the controls (72.0±3.6 kg). The diabetic patients were all participants in the Diabetes Registry program of the Washington University Diabetes Research and Training Center. None had symptomatic autonomic neuropathy. Subjects with overt heart disease, hypertension, anemia, a history of asthma, or of a convulsive disorder, proliferative retinopathy, or a serum creatinine >1.3 mg/dl were not included. All studies were performed at the Washington University Clinical Research Center and were approved by the Washington University Human Studies Committee.

Study protocol. On the day before study, patients with IDDM were treated with regular insulin only. They received a variable intravenous infusion of regular insulin, with plasma glucose measurements at least hourly, to achieve and maintain euglycemia from 1600 h on that day through 0800 h on the morning of study. The insulin infusions were discontinued at that point.

All subjects were studied after an overnight fast and in the supine position. At 0720 h, catheters for sampling and for drug infusion were inserted into antecubital veins in each arm. Regular insulin, 0.075 U/kg body wt, was given by rapid intravenous injection at 0800 h. Blood samples (9 ml) were obtained from the contralateral arm, and the blood pressure and heart rate were recorded, at 10-min intervals from 20 min before insulin injection through 200 min after insulin injection. Blood was promptly distributed to iced tubes containing heparin (500 U/ml); heparin, EGTA (5.0 mM), and reduced glutathione (5.0 mM); EDTA (4.0 mM) plus aprotinin, 500 U/ml (Trasylol, SDA Pharmaceuticals, Inc., New York.); or perchloric acid (3.0 M). These were centrifuged at 4°C and the supernatants frozen and stored at −80°C for subsequent analysis.

All subjects were studied on two separate days, once during infusion of saline and once during infusion of the β-adrenergic antagonist propranolol (Inderal, Ayerst Laboratories, Inc., New York.). These infusions were begun at 0750 h (10 min before insulin injection) and continued throughout the remainder of the study with an infusion pump (Harvard

[1] *Abbreviation used in this paper*: IDDM, insulin-dependent diabetes mellitus.

TABLE I
Patients with Insulin-dependent Diabetes Mellitus

Patient No.	Sex	Age	Hemoglobin A_{1c}*	Duration of diabetes	Complications
		yr.	%	Yr.	
1	Male	25	12.2	15	Background retinopathy, peripheral neuropathy‡
2	Female	24	7.5	13	Background retinopathy
3	Female	28	11.6	18	Peripheral neuropathy
4	Female	30	12.3	22	Background retinopathy, peripheral neuropathy
5	Male	27	12.2	15	Peripheral neuropathy
6	Female	38	12.9	12	Background retinopathy, peripheral neuropathy
7	Female	22	11.8	9	Peripheral neuropathy
8	Female	34	8.6	19	Background retinopathy, peripheral neuropathy

* Normal < 8.3%.
‡ Reduced nerve conduction velocities.

Apparatus Co., Inc., S. Natick, Mass.). The sequence was varied. The propranolol dose was 80 μg/min after a 3.0-mg dose given by rapid intravenous injection. Equivalent volumes of saline and of the propranolol containing solution were infused.

Analytical methods. Plasma glucose was measured with a glucose oxidase technique. Plasma concentrations of glucagon (13), insulin (14), growth hormone (15), and cortisol (16) were determined by radioimmunoassays. Antiserum 30K was used to measure glucagon. Free insulin was measured after polyethylene glycol precipitation (17) in all samples. Plasma epinephrine and norepinephrine were measured with a single isotope derivative method (18) using 50-μl samples. Blood glycerol (19), β-hydroxybutyrate (20), and lactate (21) were determined with microfluorometric techniques.

Statistical methods. Data are expressed as the mean plus or minus the standard error (SE). Statistical tests included Student's *t* tests for paired and unpaired data and regression analysis (22).

RESULTS

Glucose recovery from insulin-induced hypoglycemia in initially euglycemic patients with IDDM compared with nondiabetic controls (saline studies)

Plasma glucose concentrations. (Fig. 1). Mean plasma glucose concentrations at base line, before insulin injection (80±2 mg/dl in controls and 80±9 mg/dl in patients), and mean nadir plasma glucose concentrations (26±3 mg/dl in controls and 32±4 mg/dl in patients) were not significantly different. However, the plasma glucose nadir was delayed from 30 min in controls to 50 min after insulin injection in patients with IDDM.

Glucose recovery from hypoglycemia was delayed in patients with IDDM. Mean plasma glucose concentrations were significantly ($P < 0.01$) lower than those of controls from 50 through 70 min and did not become superimposable on those of controls until 120 min after insulin injection. The increments in plasma glucose levels from their nadirs were inversely related to the plasma-free insulin concentrations at 120 min ($r = 0.569$, $P < 0.02$) in diabetic patients (data not shown).

Posthypoglycemic hyperglycemia developed in patients with IDDM. At 200 min after insulin injection the mean plasma glucose concentration was 148±19 mg/dl, significantly ($P < 0.001$) higher than that of 75±1 mg/dl in controls.

Plasma concentrations of glucose regulatory and counterregulatory hormones. Mean plasma-free insulin concentrations (Fig. 1) after insulin injection tended to be higher in patients with IDDM although this apparent difference was statistically significant ($P < 0.05$) at only a single time point (30 min). These

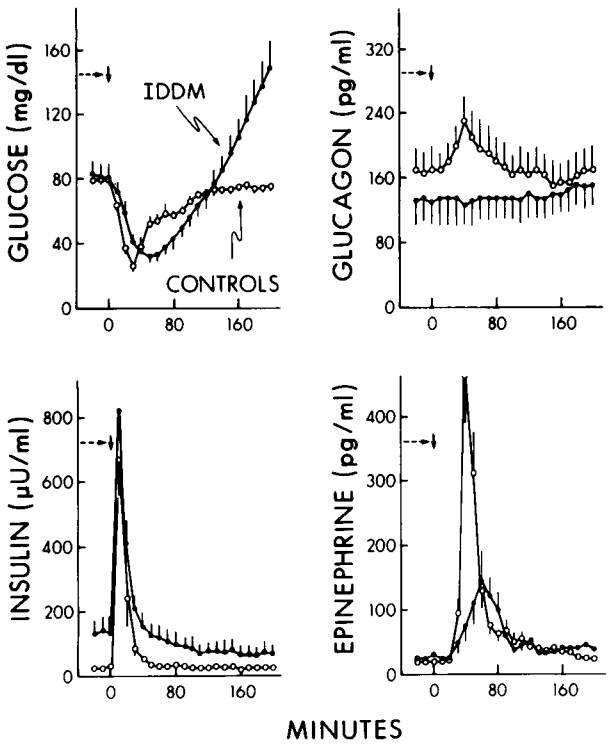

FIGURE 1 Mean (±SE) plasma glucose, free insulin, glucagon, and epinephrine concentrations before and after rapid intravenous injection of 0.075 U/kg of regular insulin (solid arrows) during saline infusion in initially euglycemic (overnight insulin-infused, interrupted arrows) patients with IDDM (filled symbols) and in nondiabetic controls (open symbols).

data were skewed by unusually high values throughout in two patients. However, these values were reproducible on repeat assay and were internally consistent on the two study days in these patients. At the end of the study, plasma-free insulin concentrations in diabetic patients were approximately half those required to maintain euglycemia before the study. The initial half-time of disappearance of injected insulin was significantly prolonged from 6.1±0.2 min in controls to 9.2±1.2 min ($P < 0.05$) in patients with IDDM.

Mean plasma glucagon concentrations (Fig. 1) rose from 170±30 pg/ml to a maximum of 229±31 pg/ml ($P < 0.02$) at 40 min after insulin injection in controls. In contrast, mean plasma glucagon concentrations did not change significantly in patients with IDDM (130±31 pg/ml before insulin injection; maximum of 136±34 pg/ml 60 min after insulin injection). The maximum mean value was significantly ($P < 0.05$) higher in controls than in diabetic patients. The maximum increments in plasma glucagon over mean base-line values averaged 14±1 pg/ml in diabetic patients, significantly ($P < 0.01$) less than those averaging 89±20 pg/ml in controls (data not shown).

Mean plasma epinephrine concentrations (Fig. 1) rose from 19±2 pg/ml to a maximum of 466±99 pg/ml ($P < 0.01$) 40 min after insulin injection in controls, but only from 29±5 pg/ml to 145±49 pg/ml at 60 min in patients with IDDM. Plasma epinephrine levels were significantly lower in diabetic patients at 40 min ($P < 0.01$) and 50 min ($P < 0.05$) after insulin injection. The maximum mean plasma epinephrine concentration was achieved 20 min later in diabetic patients and was significantly ($P < 0.02$) lower than that achieved in controls. The maximum increments in plasma epinephrine over mean base-line values averaged 180±49 pg/ml in diabetic patients, significantly ($P < 0.05$) lower than those averaging 464±101 pg/ml in controls (data not shown).

Mean plasma norepinephrine concentrations (Table II) were not significantly different in the two groups.

Mean plasma growth hormone concentrations (shown in Fig. 7) rose from 2.3±1.1 ng/ml to a maximum of 19.8±3.8 ng/ml ($P < 0.01$) in controls and from 7.5±2.0 ng/ml to a maximum of 26.9±5.8 ng/ml ($P < 0.01$) in patients with IDDM 60 min after insulin injection. The mean plasma growth hormone level was significantly ($P < 0.02$) higher at base line before insulin injection in diabetic patients, but did not differ from that of controls during the remainder of the study. The maximum increments in plasma growth hormone over mean base line averaged 24.0±5.4 ng/ml in diabetic patients and 23.5±4.6 ng/ml in controls (data not shown).

Mean plasma cortisol concentrations (shown in Fig. 8) rose from 17.6±3.1 μg/dl to a maximum of 24.9±2.7 μg/dl ($P < 0.05$) in controls and from 10.8±1.6 μg/dl to a maximum of 20.7±3.3 μg/dl ($P < 0.02$) in patients with IDDM 70 min after insulin injection. Mean plasma cortisol concentrations did not differ significantly between the two groups. The maximum increments in plasma cortisol over base line averaged 7.3±2.4 μg/dl in controls and 10.2±2.9 μg/dl (not significant) in diabetic patients (data not shown).

Blood concentrations of metabolic intermediates. (Table III). Patients with IDDM differed significantly from controls in that the initial rise in blood lactate after insulin injection did not occur and the late increment in blood β-hydroxybutyrate after insulin injection was greater in diabetic patients.

Heart rate and blood pressure. (Table II). Patients with IDDM exhibited significantly higher mean heart rates, systolic blood pressures, and diastolic blood pressures than controls. Mean heart rates increased signif-

TABLE II

Effects of Hypoglycemia with and without β-Adrenergic Blockade on Heart Rate, Blood Pressure, and Plasma Norepinephrine

	Before insulin			After insulin					
	0 min			30–60 min			200 min		
	Saline	PRP	*P*	Saline	PRP	*P*	Saline	PRP	*P*
Heart rate, per minute									
			<0.001						
Controls	64±3	60±2	NS	83±5	63±5	<0.001	65±4	58±3	<0.05
			<0.01						
IDDM	87±3	83±3	NS	96±5	81±2	<0.01	88±5	79±3	<0.01
P	<0.001	<0.001		<0.1 > 0.05	<0.01		<0.01	<0.01	
Systolic BP, *mm Hg*									
			NS						
Controls	110±3	111±3	NS	119±6	118±4	NS	110±2	108±2	NS
			<0.02						
IDDM	118±4	115±4	NS	125±4	124±3	NS	121±3	116±3	<0.05
P	0.05	NS		NS	NS		<0.01	<0.1 > 0.05	
Diastolic BP, *mm Hg*									
			NS						
Controls	67±2	70±1	NS	69±3	81±4	<0.01	70±2	71±2	NS
			NS						
IDDM	80±2	82±6	NS	82±2	88±2	<0.05	80±3	82±2	NS
P	<0.01	<0.001		<0.01	NS		<0.05	<0.01	
Norepinephrine, *pg/ml*									
			<0.05						
Controls	217±44	215±38	NS	285±31	290±54	NS	248±33	260±29	NS
			<0.1 > 0.05						
IDDM	244±57	219±75	NS	313±61	417±163	NS	305±69	247±70	NS
P	NS	NS		NS	NS		NS	NS	

PRP, propranolol; BP, blood pressure.

icantly during hypoglycemia in both groups. However, the maximum increments in heart rate over mean base line averaged only 9±2 beats/min in the diabetic patients, significantly ($P < 0.01$) less than those averaging 22±3 beats/min in controls (data not shown).

Effects of β-adrenergic blockade on glucose recovery from insulin-induced hypoglycemia and on posthypoglycemic hyperglycemia in initially euglycemic patients with insulin-dependent diabetes mellitus (propranolol studies).

Plasma glucose concentrations. (Fig. 2). β-Adrenergic blockade had no effect on the plasma glucose nadir or on glucose recovery from insulin-induced hypoglycemia in controls. In diabetic patients, nadir plasma glucose concentrations, 32±4 mg/dl during saline and 31±4 mg/dl during propranolol, also were unaffected. However, glucose recovery from hypoglycemia was significantly impaired by β-adrenergic blockade in patients with IDDM. Mean postnadir plasma glucose levels were significantly lower during propranolol than during saline from 80 min through the remainder of the study. During saline the mean postnadir plasma glucose concentration first exceeded the base-line level at 140 min after insulin injection. A similar mean glucose level was not achieved until 180 min during propranolol.

Posthypoglycemic hyperglycemia (in the time frame of this study) was largely prevented by β-adrenergic blockade. At the end of the study, 200 min after insulin injection, the mean plasma glucose concentration dur-

TABLE III

Effects of Hypoglycemia with and without β-Adrenergic Blockade on Blood Lactate, Glycerol, and β-Hydroxybutyrate

	Before insulin			After insulin					
	0 min			30–70 min			200 min		
	Saline	PRP	*P*	Saline	PRP	*P*	Saline	PRP	*P*
Lactate, *mmol/liter*									
			<0.01			<0.01			
Controls	1.02±0.11	0.89±0.14	NS	1.74±0.13	1.46±0.10	<0.05	0.89±0.07	0.81±0.06	NS
			NS			<0.05			
IDDM	1.01±0.27	1.03±0.07	NS	1.14±0.26	1.33±0.10	NS	0.75±0.10	0.86±0.06	NS
P	NS	NS		<0.02	NS		NS	NS	
Glycerol, *μmol/liter*									
			NS			<0.05			
Controls	164±35	100±10	NS	94±16	60±14	<0.01	145±22	105±16	NS
			NS			<0.02			
IDDM	159±88	112±33	NS	84±27	89±40	NS	201±40	172±63	NS
P	NS	NS		NS	NS		NS	NS	
β-Hydroxybutyrate, *μmol/liter*									
			<0.01			<0.001			
Controls	185±37	179±52	NS	70±14	56±9	NS	369±57	208±37	<0.01
			<0.02			<0.001			
IDDM	263±75	197±45	NS	109±18	86±9	NS	1,260±209	586±213	<0.001
P	NS	NS		<0.02	<0.05		<0.01	NS	

PRP, propranolol.

ing saline was 148±19 mg/dl; that during propranolol was 96±24 mg/dl ($P < 0.001$).

Patients with IDDM were heterogeneous with respect to the degree to which β-adrenergic blockade limited the postnadir rise in plasma glucose (Fig. 3). The glucose rise was unaltered in one patient, minimally reduced in two patients, and substantially reduced in five patients. The magnitude of the post-nadir increase in plasma glucose was related to the degree of residual glucagon secretion in that the increments in plasma glucose during propranolol, expressed as a percentage of those during saline, were correlated with the maximum increments in plasma glucagon concentrations over mean base-line values ($r = 0.606$, $P < 0.02$) in individual patients (data not shown). These post nadir increments in plasma glucose levels were inversely related to plasma-free insulin concentrations at 200 min ($r = 0.553$, $P < 0.05$) (data not shown).

Plasma concentrations of glucose regulatory and counterregulatory hormones. Mean plasma insulin concentrations (Fig. 4) and the initial disappearance rate of injected insulin were unaffected by β-adrenergic blockade. In controls the initial half-times of disappearance of injected insulin were 6.1±0.2 min during saline and 6.4±0.4 min during propranolol. Corresponding values in patients with IDDM were 9.2±1.2 min and 10.0±1.3 min.

Mean plasma glucagon concentrations (Fig. 5) were also unaffected by β-adrenergic blockade.

In association with hypoglycemia, mean plasma epinephrine concentrations were elevated by β-adrenergic blockade (Fig. 6). Due to scatter in the data, apparent elevations were not statistically significant at all time points. However, mean plasma epinephrine concentrations were significantly higher during propranolol than during saline at 60, 70, 120, 130, 140, 150, 170, and 180 min after insulin injection in controls and at 90 and 100 min in diabetic patients.

Mean plasma norepinephrine concentrations (Table II) were not significantly altered by β-adrenergic blockade although plasma norepinephrine levels during hypoglycemia tended to be higher during propranolol than during saline.

Mean plasma growth hormone levels in association

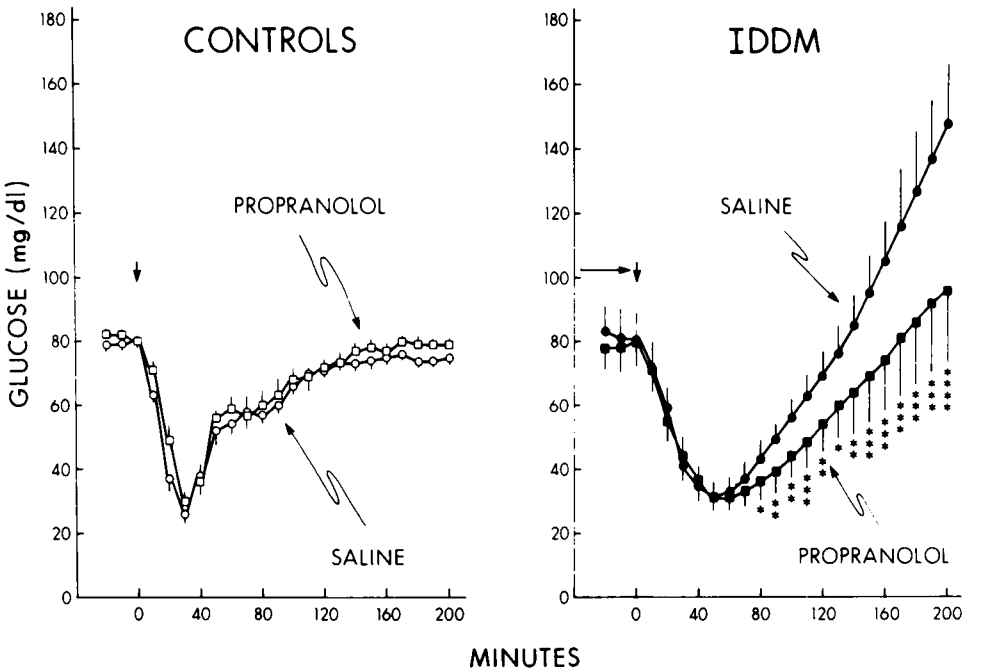

FIGURE 2 Mean (±SE) plasma glucose concentrations before and after rapid intravenous injection of 0.075 U/kg of regular insulin (vertical arrows) during infusion of saline and of propranolol in nondiabetic controls and in initially euglycemic (overnight insulin-infused, horizontal arrow) patients with IDDM. The asterisks denote P values of $<0.05^{*}$, $<0.02^{**}$, $<0.01^{***}$, and $<0.001^{****}$.

with hypoglycemia were significantly increased by ~50% in controls and nearly 100% in patients with IDDM by β-adrenergic blockade (Fig. 7).

Mean plasma cortisol concentrations (Fig. 8) were not significantly altered by β-adrenergic blockade.

Blood concentrations of metabolic intermediates. (Table III). β-Adrenergic blockade significantly reduced the posthypoglycemic rise in blood β-hydroxybutyrate, by ~50%, in both controls and patients with IDDM; it also tended to blunt the late rise in blood glycerol.

Heart rate and blood pressure. (Table II). Hypoglycemic increments in heart rates were prevented by β-adrenergic blockade in both controls and patients with IDDM. β-Adrenergic blockade resulted in significantly higher mean diastolic blood pressures during hypoglycemia in both groups. Systolic blood pressures were unaffected.

DISCUSSION

Compared to nondiabetic controls, initially euglycemic (overnight insulin-infused) patients with IDDM exhibited a similar, but somewhat delayed, plasma glucose nadir, delayed glucose recovery from hypoglycemia and posthypoglycemic hyperglycemia after the rapid intravenous injection of 0.075 U/kg of regular insulin. Delayed glucose recovery from hypoglycemia in diabetic patients was associated with, and potentially attributable to, three factors. First, as previously reported (5–8), the plasma glucagon response to hypoglycemia was markedly blunted in the diabetic patients. Second, the adrenomedullary response to hypoglycemia was partially reduced in the patients with IDDM; mean maximum plasma epinephrine concentrations were approximately one-third those achieved in nondiabetic controls. This could well be a manifestation of diabetic autonomic neuropathy in these patients with longstanding diabetes. Hilsted et al. (23) recently demonstrated reduced plasma epinephrine responses to hypoglycemia in diabetics selected for autonomic neuropathy compared with those without autonomic neuropathy. The finding of higher resting heart rates in our diabetic patients is consistent with the presence of parasympathetic neuropathy. Their smaller increments in heart rate during hypoglycemia could be due to their reduced epinephrine responses or to diminished norepinephrine release from sym-

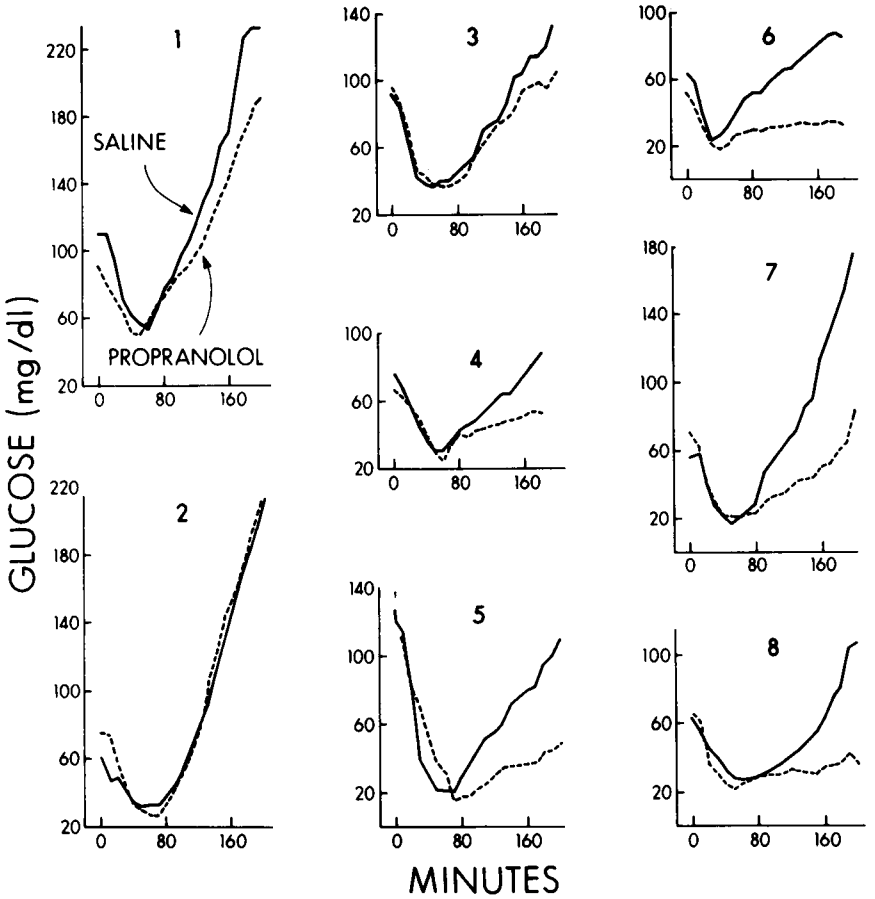

FIGURE 3 Plasma glucose concentrations before and after rapid intravenous injection of 0.075 U/kg of regular insulin (at 0 min) in initially euglycemic patients with IDDM. Data denoted by solid lines were obtained during infusion of saline, those denoted by interrupted lines during infusion of propranolol.

pathetic neurons innervating the heart. With respect to the latter, however, plasma norepinephrine responses to hypoglycemia were not discernibly reduced in the diabetic patients.

It should be emphasized that the reduced adrenomedullary response was found during hypoglycemia, a potent stimulus to epinephrine secretion. In previous studies, we did not find a reduced plasma epinephrine response to standing in diabetic patients with documented adrenergic neuropathy (24), nor did we find reduced basal or posturally stimulated plasma epinephrine concentrations to be a feature of diabetes per se (25). Nonetheless, if it is a reflection of diabetic adrenergic neuropathy, the finding of a reduced plasma epinephrine response to hypoglycemia indicates some involvement at the level of the postganglionic cell bodies or their more central connections although the major involvement is thought to lie more distally in the postganglionic axons (24).

Diminished clearance of injected insulin is the third factor of potential importance to delayed glucose recovery from hypoglycemia in patients with IDDM. The initial half-time of disappearance of injected insulin was prolonged in the diabetic patients and the increments in plasma glucose from their nadirs were inversely related to the plasma-free insulin concentrations in individual patients during the glucose recovery phase. Clearly, the relative importance of each of these factors—markedly diminished glucagon secretion, partially reduced epinephrine secretion, and reduced clearance of injected insulin—to the observed delay in glucose recovery from hypoglycemia in patients with IDDM remains to be established.

Posthypoglycemic hyperglycemia in patients with

IDDM was also associated with, and potentially attributable to, three factors. The mean plasma free insulin concentration during the hyperglycemic phase was approximately half that required to maintain euglycemia prior to study; hence, lower circulating insulin levels were undoubtedly an important factor in the pathogenesis of posthypoglycemic hyperglycemia. Also, it is conceivable that the small amounts of glucagon released could have contributed to increased hepatic glucose production, particularly since measurements were made in the peripheral, rather than the portal, circulation. Lastly, although the plasma epinephrine response was reduced compared with that of nondiabetic controls, the patients with IDDM released substantial amounts of epinephrine in response to hypoglycemia. The contribution of β-adrenergic stimulation to the development of posthypoglycemic hyperglycemia in the diabetic patients was tested directly in this study as discussed later.

Infusion of the β-adrenergic antagonist propranolol produced effective β-adrenergic blockade as evidenced by prevention of the tachycardic response to hypoglycemia, by occurrence of a diastolic pressor response during hypoglycemia and by blunting of the posthypoglycemic rise in blood β-hydroxybutyrate

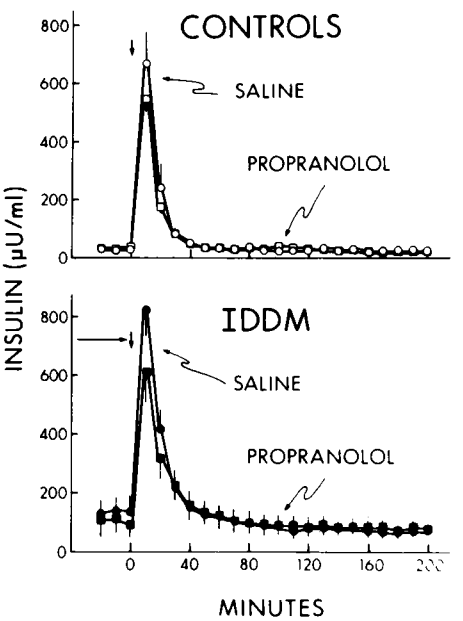

FIGURE 4 Mean (±SE) plasma free insulin concentrations before and after rapid intravenous injection of 0.075 U/kg of regular insulin (vertical arrows) during infusion of saline and of propranolol in nondiabetic controls and in initially euglycemic (overnight insulin-infused, horizontal arrow) patients with IDDM.

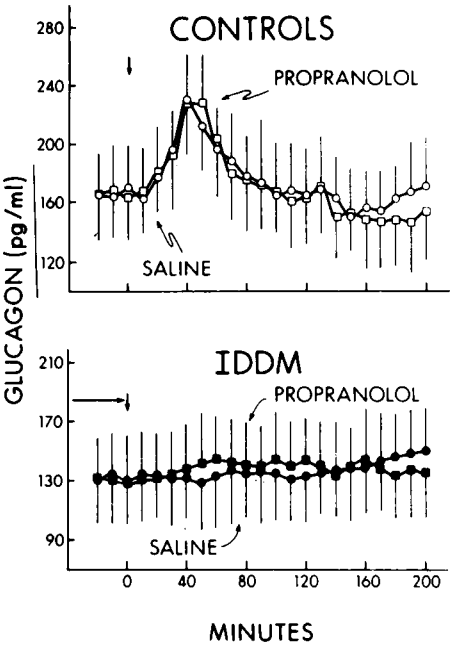

FIGURE 5 Mean (±SE) plasma glucagon concentrations before and after rapid intravenous injection of 0.075 U/kg of regular insulin (vertical arrows) during infusion of saline and of propranolol in nondiabetic controls and in initially euglycemic (overnight insulin-infused, horizontal arrow) patients with IDDM.

concentrations in both controls and in patients with IDDM. In association with hypoglycemia, plasma epinephrine concentrations were elevated during β-adrenergic blockade. This is, at least at part, due to the sharp reduction in the clearance of epinephrine from the circulation that occurs during β-adrenergic blockade (26). Importantly, neither the plasma insulin concentrations nor the initial half-times of disappearance of injected insulin were altered by β-adrenergic blockade. Similarly, plasma glucagon and cortisol levels were unaffected. The plasma growth hormone responses to hypoglycemia were augmented during β-adrenergic blockade, as previously reported (27).

In nondiabetic controls, recovery from insulin-induced hypoglycemia was unaffected by β-adrenergic blockade. This has been a consistent finding in our studies (1, 3) and is part of the evidence supporting the conclusion that epinephrine secretion is not critical to glucose recovery from hypoglycemia except when glucagon secretion is deficient (1–4). In contrast, glucose recovery from hypoglycemia was significantly impaired during β-adrenergic blockade in patients with IDDM. This finding confirms our hypothesis that such patients are more dependent upon epinephrine-me-

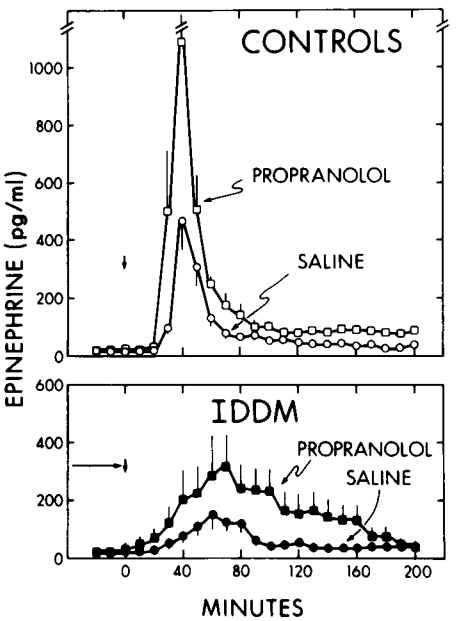

FIGURE 6 Mean (±SE) plasma epinephrine concentrations before and after rapid intravenous injection of 0.075 U/kg of regular insulin (vertical arrows) during infusion of saline and of propranolol in nondiabetic controls and in initially euglycemic (overnight insulin-infused, horizontal arrow) patients with IDDM.

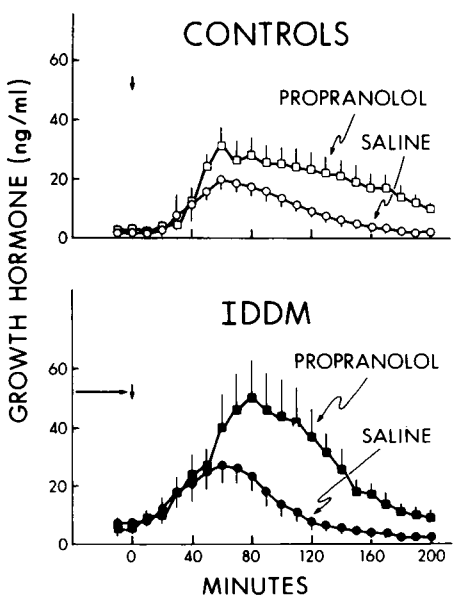

FIGURE 7 Mean (±SE) plasma growth hormone concentrations before and after rapid intravenous injection of 0.075 U/kg of regular insulin (vertical arrows) during infusion of saline and of propranolol in nondiabetic controls and in initially euglycemic (overnight insulin-infused, horizontal arrow) patients with IDDM.

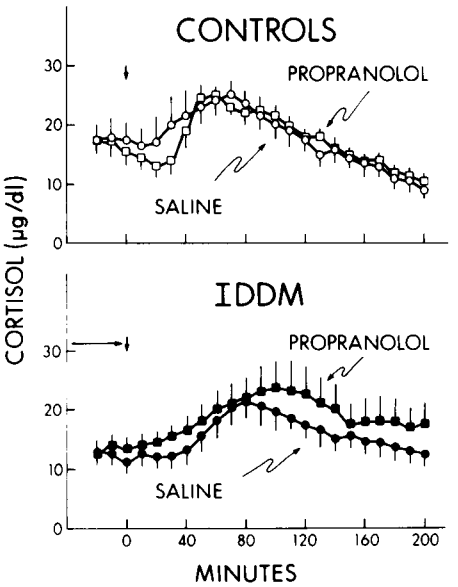

FIGURE 8 Mean (±SE) plasma cortisol concentrations before and after rapid intravenous injection of 0.075 U/kg of regular insulin (vertical arrows) during infusion of saline and of propranolol in nondiabetic controls and in initially euglycemic (overnight insulin-infused, horizontal arrow) patients with IDDM.

diated β-adrenergic mechanisms to promote glucose recovery from hypoglycemia than are nondiabetic persons and indicates that the measured deficiency of glucagon secretion in response to hypoglycemia is functionally important in patients with IDDM. The latter conclusion is similar to that of Campbell, Kraegen, and Lazarus (28) who observed that insulin infusion ultimately results in lower mean blood glucose levels, with smaller increments in mean plasma glucagon, in insulin requiring patients with diabetes compared with nondiabetic controls.

Further, in the time frame of our studies, posthypoglycemic hyperglycemia was largely prevented by β-adrenergic blockade. This finding indicates that sympathoadrenal activation, coupled with insulin deficiency, plays an important role in the pathogenesis of this phenomenon.

There was considerable heterogeneity among the diabetic patients with respect to the degree to which β-adrenergic blockade limited the posthypoglycemic rise in plasma glucose. This may relate, in part, to the degree of residual glucagon secretion since postnadir increments in plasma glucose were significantly correlated with maximum increments in plasma glucagon in individual patients. Again, circulating insulin levels are of likely importance; postnadir increments in

plasma glucose were inversely related to plasma-free insulin concentrations at the end of the study.

These findings have both practical and theoretical implications. Propranolol is a drug that is widely prescribed for the treatment of disorders, such as hypertension and ischemic heart disease, that occur commonly in patients with IDDM. If treated with this drug, many such patients will be at increased risk for serious hypoglycemia that may not be recognized until neuroglycopenia becomes clinically evident since propranolol may also prevent some of the adrenergic symptoms of hypoglycemia. The findings also provide additional theoretical insight into both the beneficial and the detrimental effects of sympathoadrenal activation on metabolic control in patients with IDDM. Lastly, they provide further support for our model (1–4) of the mechanisms of hypoglycemic glucose counterregulation.

In summary, we conclude that patients with IDDM are, to varying degrees, dependent upon epinephrine-mediated β-adrenergic mechanisms to promote glucose recovery from hypoglycemia, that the degree of this dependence upon epinephrine is an inverse function of the residual capacity to secrete glucagon in response to hypoglycemia in individual patients and that sympathoadrenal activation, coupled with the inability to secrete insulin, plays an important role in the pathogenesis of posthypoglycemic hyperglycemia in patients with IDDM.

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