The Regulation of Plasma Ketone Body Concentration by Counterregulatory Hormones in Man

I. Effects of Norepinephrine in Diabetic Man

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SUMMARY

Previous studies have attributed norepinephrine's ketogenic activity to its ability to mobilize peripheral fat stores. This study was designed to determine whether norepinephrine has ketogenic activity independent of its lipolytic effect in diabetic man.

Six insulin-dependent diabetic subjects were infused with pathophysiologic concentrations of norepinephrine (0.08 μg./kg./min.). As a control for norepinephrine's lipolytic effect, a separate heparin-induced free fatty acid generation study was performed on each subject. The results demonstrate, for the first time in man, that norepinephrine has ketogenic activity independent of its lipolytic effect. Furthermore, physiologic elevations of norepinephrine concentration were also demonstrated to increase plasma glucagon concentration. Our data are consistent with the possibility that the rise in concentration of glucagon may have a participated in the catecholamine-augmented ketogenesis. DIABETES ***26*:989-96, October, 1977.**

Diabetic ketoacidosis is characterized by an elevation of plasma norepinephrine concentration in addition to other counterregulatory hormones, and this catecholamine elevation is proportional to the severity of the metabolic derangement.[1] Infusions of catecholamines in diabetic subjects have resulted in the elevation of plasma ketone body concentration, and this effect has been attributed to the catecholamine-induced rise in plasma free fatty acid substrate.[2,3] If norepinephrine had no effect on ketogenesis other than through augmentation of free fatty acid availability, then the rise in plasma ketone body concentration should be proportional to the degree of catecholamine-induced lipolysis. However, additional studies have suggested that the rise in plasma ketone body concentration in diabetic man is greater than that which can be accounted for by the rise in plasma free fatty acid substrate concentration.[4] This suggestion has been supported by in-vitro experiments both in the perfused liver[5,6] and in isolated hepatocytes,[7] in which a direct ketogenic action of catecholamines has been demonstrated. Based on these experiments, the present study was undertaken to resolve the question of whether norepinephrine exerts an in-vivo ketogenic action independent of its lipolytic effect at the adipocyte.

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METHODS

Patient Population

Six healthy insulin-dependent diabetic subjects (three male and three female) on weight-maintaining ADA diets were studied. Ages ranged from 21 to 60 years. All subjects were within 10 per cent of their ideal body weight by the Metropolitan Life Insurance Company Tables.[8] All subjects had at least one past medically documented episode of ketoacidosis requiring hospitalization. However, throughout the duration of the study, all subjects remained in good health and no change in their daily insulin dosage occurred. Insulin dosage ranged from 33 to 60 units of NPH U100 insulin subcutaneously at 8:30 a.m. daily. All subjects were deficient in endogenous insulin secretion as defined by the failure of plasma free insulin concentration to increase more than 4.0 μU./ml. in any subject following intravenous administration of 10.0 gm. of glucose as previously described.[9]

STUDY PROTOCOL

Each subject participated in both a control-heparin and a norepinephrine-infusion study separated by an interval of at least seven days. All studies were completed between 6:00 a.m. and 8:00 a.m. after an overnight fast and approximately 24 hours from the subject's last therapeutic insulin injection. On the morning of the study, the subject assumed the supine position and one indwelling 19-gauge venous catheter was inserted into an antecubital vein of each arm, maintained patent by a microinfusion of normal saline (1 ml./min.). All blood samples were withdrawn from one intravenous catheter, and, following the baseline period, either heparin (in the control-heparin study) or norepinephrine (in the norepinephrine-infusion study) was administered into the contralateral arm via the indwelling catheter.

Each study required 90 minutes to complete. The initial 30 minutes of the study is termed the baseline period and the terminal 60 minutes the experimental period. The blood sample drawn immediately prior to the experimental period (+29 minutes) is termed the basal concentration and is the concentration with which changes in the experimental period were compared. Throughout the entire study period serial 10-ml. blood specimens were withdrawn as detailed in tables 1 and 2 so that a total of 140 ml. of blood was withdrawn and a total of 180 ml. of normal saline infused. In the control-heparin study, 5,000 units of sodium heparin (Lipo-heparin, Riker Laboratories, Inc., Northridge, California) were administered as an intravenous bolus immediately following the initial 30-minute baseline period to increase plasma free fatty acid concentration.[10] Immediately following the baseline period in the norepinephrine-infusion study, intravenous administration of norepinephrine was begun (Levophed, Winthrop Laboratories, New York, N. Y.). A bolus injection of 15 μg. over a one-minute period was followed by a constant intravenous infusion of norepinephrine (0.08 μg./kg./min.) for the remaining 59 minutes of the experimental period. Immediately prior to administration, the norepinephrine was diluted in 250 ml. of normal saline containing 2 per cent human albumin at a concentration that would deliver 0.08 μg./kg./min. when infused at a rate of 1.0 ml./min. The infusion of this quantity of norepinephrine has been reported to result in a plasma concentration of 1.5 to 2.0 ng./ml.,[11] a plasma concentration that may be attained in severe diabetic ketoacidosis.[1]

TABLE 1

Plasma concentration of ketone bodies in six diabetic subjects during control-heparin and norepinephrine-infusion studies

	Baseline period				(Basal) (sample)		Experimental period (minutes)							
	−30	−25	−20	−10	−1	+2	+5	+10	+15	+20	+30	+40	+50	+60
Control														
S.P.	648	823	870	942	931	875	849	1,004	1,482	1,219	1,250	1,158	993	880
W.M.	180	242	252	314	355	314	339	499	536	669	813	772	735	699
J.G.	396	427	468	468	442	432	426	520	653	730	756	767	895	715
J.D.	349	463	412	457	427	421	391	576	684	920	1,019	1,091	977	936
M.C.	206	247	236	303	278	257	267	263	344	365	401	447	340	232
S.G.	638	730	736	674	663	659	699	849	972	1,085	1,322	1,451	1,523	1,533
Mean AcAc	131	151	160	173	168	173	172	187	216	242	255	260	249	242
Mean BOH	272	338	335	353	348	320	323	431	569	589	672	688	662	591
Mean total KB	403	489	496	526	516	493	495	618	778	831	927	948	910	832
Norepinephrine infusion														
S.P.	684	802	916	947	972	880	1,008	1,137	1,271	1,394	1,657	1,821	1,857	1,883
W.M.	144	185	200	231	247	175	180	273	299	324	628	807	880	957
J.G.	267	277	263	283	308	308	329	427	525	757	1,070	1,297	1,476	1,666
J.D.	406	510	520	453	381	314	334	443	499	601	787	997	1,327	1,549
M.C.	288	396	391	404	414	437	452	514	633	664	823	853	906	931
S.G.	386	436	478	499	474	427	540	772	890	1,358	1,893	2,475	2,958	3,576
Mean AcAc	123	147	159	160	159	131	158	194	203	232	294	335*	371*	426*
Mean BOH	240	287	303	309	307	292	316	400	483	618	849	1,040*	1,196*	1,334*
Mean total KB	363	434	461	469	466	424	473	594	686	849	1,143	1,375*	1,569*	1,760*

*Signifies that the change in concentration from baseline (+30 minutes) in the norepinephrine-infusion study is statistically greater than the change in concentration from baseline in the control study ($P < 0.05$).

→Time point at which either bolus intravenous heparin (5,000 U.) was administered in the control-heparin study or norepinephrine-infusion study (0.08 μg./kg./min.) was begun in the norepinephrine-infusion study.

TABLE 2

Plasma concentration of substrates and hormones in six diabetic subjects during control and norepinephrine-infusion studies

	Baseline period				(Basal) (sample)	Experimental period (minutes)								
	−30	−25	−20	−10	−1	+2	+5	+10	+15	+20	+30	+40	+50	+60
Control														
Free fatty acid	978	969	916	975	933	1,906	1,957	2,186	1,897	1,853	1,653	1,276	1,298	1,116
μmol/L.	±110	±117	±102	±56	±115	±246	±269	±310	±249	±267	±243	±177	±200	±131
Glucose	178	184	181	180	183	184	188	179	182	183	187	177	181	187
mg./dl.	±38	±40	±40	±37	±39	±41	±43	±41	±43	±42	±41	±40	±40	±41
Glucagon	71	72	71	68	73	76	75	80	77	72	67	61	63	67
pg./ml.	±7	±6	±6	±6	±6	±11	±3	±12	±10	±3	±6	±6	±5	±7
Growth hormone	9	7	7	9	12	9	6	10	6	10	10	10	15	17
ng./ml.	±3	±2	±3	±5	±6	±5	±2	±4	±3	±5	±5	±6	±9	±11
Cortisol	15	17	15	13	12	12	13	13	13	13	11	12	10	12
μg./dl.	±3	±3	±3	±3	±2	±2	±3	±3	±3	±3	±3	±2	±3	±3
Insulin	23	24	25	28	27	26	28	26	24	26	25	26	22	25
μU./ml.	±3	±2	±2	±5	±3	±2	±4	±2	±3	±3	±2	±3	±2	±2
Norepinephrine infusion														
Free fatty acid	891	848	874	876	824	974*	1,069*	1,232*	1,284*	1,391	1,578	1,520	1,588	1,482*
μmol/L.	±100	±84	±96	±79	±101	±138	±161	±182	±195	±228	±234	±246	±329	±272
Glucose	208	204	203	200	204	197	204	212	206	213	223	229*	234*	244*
mg./dl.	±31	±31	±30	±30	±30	±29	±29	±29	±27	±27	±27	±25	±25	±26
Glucagon	66	63	71	64	66	70	78	95	102*	96*	134*	110*	112*	114*
pg./ml.	±4	±7	±4	±4	±3	±5	±3	±10	±14	±11	±31	±16	±16	±15
Growth hormone	3	4	5	10	16	18	18	16	11	6	11	6	7	8
ng./ml.	±1	±1	±2	±4	±8	±10	±8	±8	±5	±2	±5	±3	±5	±5
Cortisol	14	14	12	11	10	10	9	9	10	8	7	8	8	8
μg./dl.	±1	±1	±1	±1	±1	±1	±1	±2	±1	±1	±1	±2	±3	±2
Insulin	24	22	24	24	24	23	22	21	20	22	25	24	24	23
μU./ml.	±5	±3	±4	±5	±4	±5	±4	±4	±4	±2	±4	±3	±4	±3

*Signifies that the change in concentration from baseline (+30 minutes) in the norepinephrine-infusion study is statistically different from the change in concentration from baseline in the control study ($P < 0.05$).

→Time point at which either bolus intravenous heparin (5,000 U.) was administered in the control-heparin study or norepinephrine-infusion study (0.08 μg./kg./min.) was begun in the norepinephrine-infusion study.

ASSAY OF SUBSTRATES AND HORMONES

All plasma samples were collected in 10-ml. heparinized glass test tubes containing, as a preservative, 100 ml. of 1.0 molar benzamidine as previously reported[12] and immediately chilled to 4° C. Acetoacetate and betahydroxybutyrate were assayed on the day of study. All other substrates and hormones were assayed in duplicate from individually frozen samples within three weeks of collection. Assays for glucose, acetoacetate, betahydroxybutyrate, and free fatty acid concentration were performed as previously described.[9]

To be certain that the lipolytic response following heparin injection occurred in vivo and not in vitro following blood withdrawal, we compared the plasma free fatty acid concentration collected as described above (heparin plus benzamidine at 4° C.) to the plasma free fatty acid concentration when collected in EDTA 1.0 mmol/L.[13] and protamine 0.5 mg./ml.,[14] two inhibitors of plasma lipoprotein lipase. This comparison was done on the day of study and at one and three weeks following the study, during which the plasma samples remained frozen at −20° C. Our results demonstrated that, when assayed on the day of study, there was no difference between the plasma free fatty acid concentration collected in heparin and benzamidine and that collected in EDTA and protamine. When assayed at one week poststudy, plasma FFA concentration was not altered by storage or by EDTA and protamine. At three weeks, similar FFA concentrations were as observed at one week and immediately following the study ($p > 0.05$). Thus, within the limits of detection of our free fatty acid assay (± 5 per cent), we were unable to detect any lipolysis occurring in vitro.

Plasma insulin concentration was assayed by

radioimmunoassay employing double-antibody precipitation[15] with a kit from Amersham Searle, Boston, Massachusetts, following removal of endogenous insulin antibody with 25 per cent polyethylene glycol.[16] In our laboratory, throughout a range of insulin concentrations from 10 to 1,000 μU./ml., a recovery of 76 ± 6 per cent was observed, as previously reported.[17] Plasma cortisol was assayed by radioimmunoassay by the method of Foster.[18] Plasma glucagon was assayed as previously described[19] with 30 K antibody obtained from Dr. Roger Unger, Veterans Administration Hospital, Dallas, Texas. Growth hormone was assayed by Dr. Glenn Peake at our institution as previously described.[20] Statistics were performed utilizing Student's *t*-test for paired data.[21] Integration of the area under a curve was calculated utilizing a Hewlett-Packard 9815 computer.

RESULTS

Substrates (Mean ± S.E.M.)

Plasma ketone body concentration (table 1, figure 1). Mean plasma ketone body concentration during the baseline period was not statistically different in the control-heparin study (basal concentration = 516 ± 98 μmol/L.) from that of the norepinephrine-infusion study (basal concentration = 466 ± 106 μmol/L.) ($p > 0.05$). During this 30-minute baseline period, a gradual elevation in mean plasma total ketone body concentration was observed in both studies as depicted in figure 1 and tabulated individually in table 1.

Following the administration of either heparin or norepinephrine, a twofold or greater elevation in plasma ketone body concentration was observed. This elevation is given for the individual diabetic subjects in table 1 and depicted as the mean rise in figure 1. The integrated rise above basal concentration in the norepinephrine-infusion study (37,890 ± 9,994 μmol/L./min.) was statistically greater than the integrated rise above basal concentration in the control-heparin study (18,008 ± 4,281 μmol/L/min.) $p < 0.05$, figure 1. Table 1 demonstrates that each diabetic subject obtained a greater maximal plasma ketone body concentration during the norepinephrine-infusion study than during his paired heparin-control study.

Plasma free fatty acid concentration (figure 1, table 2). Plasma free fatty acid concentration was not statistically different during the baseline period in the control-heparin study (basal concentration 933 ± 115 μmol/L.) from that of the norepinephrine-infusion study (basal concentration 824 ± 101 μmol/L.) $p > 0.05$. During this 30-minute baseline period, a slight decline in mean plasma free fatty acid concentration was observed in both studies as demonstrated in table 2.

As depicted in figure 1, following the administration of either heparin or norepinephrine, an elevation of plasma free fatty acids was observed. In the control-heparin study, the maximal plasma free fatty acid concentration (2,186 ± 310 μmol/L.) was attained at 10 minutes after heparin injection and gradually declined toward basal concentration during the terminal 50 minutes of the study. Following the initiation of norepinephrine infusion, the rise in plasma free fatty acid concentration was more delayed than in the control-heparin study, with a plateau observed between 20 and 50 minutes after initiation of infusion. The integrated area above basal concentration in plasma free fatty acid concentration in the control-heparin study (39,689 ± 8,493 μmol/L./min.) was not statistically different from the integrated area above basal concentration in the norepinephrine-infusion study (35,350 ± 10,469

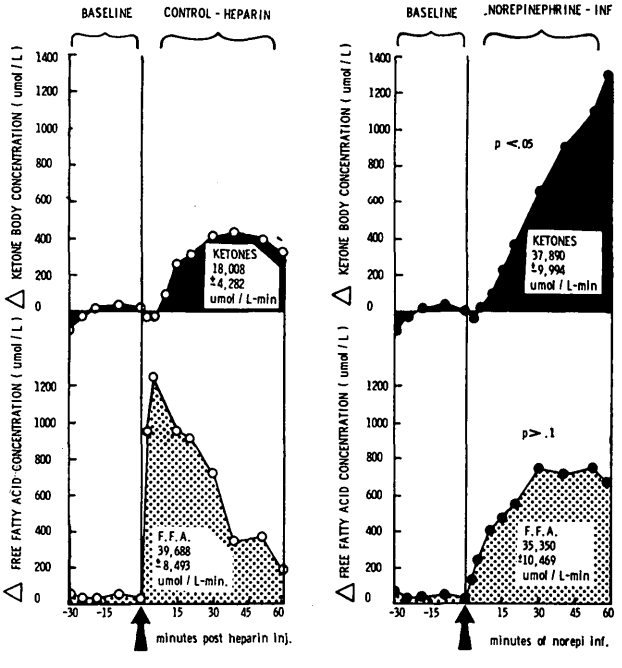

FIG. 1. The ketogenic effect of norepinephrine in diabetic man. The integrated area above basal plasma ketone body concentration (top panels) in the norepinephrine-infusion study (right) was significantly greater than in the heparin-control study (left), $p < 0.05$. In contrast, the integrated area above basal plasma free fatty acid concentration (bottom panels) in the norepinephrine study (right) was not statistically different from that in the control-heparin study (left) $p > 0.1$.

μmol/L./min.) $p > 0.1$. Since the hepatic uptake of free fatty acids from the plasma is directly proportional to the plasma concentration over the physiologic range,[22] the significantly greater hyperketonemia observed following norepinephrine-infusion compared to the control-heparin study cannot be accounted for by a difference in total plasma free fatty acid availability between the two studies (see DISCUSSION).

Plasma Glucose Concentration (Table 2)

Basal plasma glucose in the control-heparin study (183 ± 39 mg./dl.) was not different from the basal plasma glucose concentration in the norepinephrine-infusion study (204 ± 30 mg./dl.) $p > 0.05$, table 2. In contrast, during the experimental period, a significant elevation in plasma glucose above basal concentration was observed in the norepinephrine-infusion study (maximal plasma concentration = 244 ± 26 mg./dl.) compared with the control-heparin study (maximal plasma concentration = 187 ± 41 mg./dl.) $p < 0.01$.

HORMONES

Plasma Free Insulin Concentration (μU./ml.)

Mean plasma free insulin concentration, which is given in table 2, was not different at any observation point when the heparin-control study was compared with the norepinephrine-infusion study ($p > 0.05$). This concentration of free insulin of approximately 25 μU./ml. is similar to the concentration of free insulin previously reported in insulin-deficient diabetics 24 hours following their last therapeutic dose of NPH insulin.[10] Since these subjects were insulin-deficient (see METHODS), all circulating plasma free insulin was assumed to be derived from exogenous origin. If this were true, then no depression of plasma insulin following norepinephrine infusion would be expected, as has been observed for endogenously secreted insulin in normal subjects.[23]

Plasma Glucagon Concentration (Table 2)

Basal plasma glucagon concentration in the control-heparin study (73 ± 6 pg./ml.) was not statistically different from the corresponding concentration in the norepinephrine-infusion study (66 ± 3 pg./ml.) $p > 0.05$. As demonstrated in table 2, heparin administration did not alter the plasma concentration of glucagon during the terminal 60 minutes of the control-heparin study. In contrast, the infusion of norepinephrine resulted in a progressive twofold elevation of plasma glucagon concentration above basal concentration that was statistically significant at six time points of observation ($p < 0.05$).

Plasma Cortisol Concentration (Table 2)

Plasma cortisol concentration was not different in the control-heparin study from that of the norepinephrine study during the baseline period (table 2) $p > 0.05$. Throughout the duration of both studies, a progressive decline in plasma cortisol concentration was observed that began prior to the experimental period.

Plasma Growth Hormone Concentration (Table 2)

Plasma growth hormone concentration was variable but not statistically different throughout both the control-heparin study and the norepinephrine-infusion study ($p > 0.05$) when compared either as absolute difference or change from basal.

DISCUSSION

Plasma free fatty acids (FFA) are the principal substrate for hepatic ketogenesis, and their elevation results in an increase in the plasma concentration of ketone bodies in both normal and diabetic man.[10,24] Our study demonstrates that norepinephrine infusion in diabetic man results in lipolysis and the subsequent elevation of plasma ketone body concentration. However, when compared with a similar integrated rise in plasma FFA induced by heparin in the control study, the magnitude of the increase in plasma ketone body concentration following norepinephrine was significantly augmented. This observation extends to diabetic man previous in-vitro studies that demonstrated a ketogenic action of catecholamines independent of their lipolytic effect.[5-7] However, the mechanism(s) responsible for this additional ketonemic effect in vivo are not resolved and may entail a direct or an indirect action of norepinephrine on hepatic ketogenesis and/or peripheral ketone body utilization. If an indirect action of norepinephrine is a factor in the augmented ketogenesis, our observations suggest that the norepinephrine-induced increase in endogenous glucagon may participate. This latter hormone has been previously reported to have direct hepatic ketogenic activity in diabetic man.[10]

The suggestion that norepinephrine exerts a ketogenic action in diabetic man independent of its lipolytic effect is based on the assumption that plasma free fatty acid availability to support hepatic ketogenesis was not different in the control-heparin versus the norepinephrine-infusion study. This was true when the plasma free fatty acid availability was calculated as the integrated area above basal concentration, as shown in figure 1. However, figure 1 also

demonstrates that the time course of plasma free fatty acid availability was markedly different in the two studies since plasma free fatty acid concentration rose and declined earlier in the control-heparin study than in the norepinephrine-infusion study. Since we have previously demonstrated that in man the maximal rise in plasma ketone body concentration following the maximal rise in plasma free fatty acid concentration requires approximately 20 minutes,[25] this delay would favor increased ketogenesis in the heparin-control study. However, additional studies in which the magnitude and the time course of free fatty acid availability are identical in both a control and norepinephrine study will be necessary to confirm the ketogenic effect of norepinephrine.

Our interpretation that norepinephrine has ketogenic activity independent of its lipolytic effect also assumes that the hepatic uptake of free fatty acids from the plasma is proportional to their concentration. In-vitro liver perfusion experiments have demonstrated that the hepatic uptake of free fatty acids is directly proportional to their perfusate concentration throughout the physiologic range.[22] This observation has been confirmed in vivo in norepinephrine-infused dogs in which the hepatic uptake of labeled free fatty acids was proportional to their plasma concentration.[26] In contrast, liver perfusion experiments by Heimberg,[5] however, suggest that both epinephrine and norepinephrine actually decrease the uptake of plasma free fatty acids by the liver. If this were true in vivo, in man, then intrahepatic free fatty acid availability might be reduced during norepinephrine challenge relative to heparin challenge, independently of the similar exposure to plasma fatty acid elevation. If such an event occurred, then our demonstration of augmented ketogenesis during norepinephrine infusion would reflect an even greater fractional conversion of hepatic free fatty acids to ketones than observed.

If a direct effect of norepinephrine is operative in the elevation of plasma ketone bodies, at least three potential mechanisms may be suggested. First, norepinephrine may stimulate lipolysis within hepatic tissue, thereby providing FFA substrate for ketogenesis in addition to that derived from circulating plasma FFA. Catecholamines have previously been demonstrated to induce lipolysis both in heart muscle[27] and rat diaphragm in vitro.[28] Although norepinephrine infusion has been shown to result in increased hepatic lipid stores,[5] it is not known whether this quantity of newly formed triglyceride is actually less than that observed following heparin-induced free fatty acid generation. Further studies utilizing radiolabeled free fatty acids and their conversions to ketone bodies will be necessary to resolve this possibility. Secondly, catecholamines may directly stimulate hepatic conversion of FFA to ketone bodies. Three studies have been reported that examine this possibility. Cole and Margolis,[7] utilizing isolated rat hepatocytes, demonstrated that epinephrine (1×10^{-5} M) added to the incubation flask increased the conversions of I-^{14}C-palmitate to ketone bodies by 78 per cent. In addition, Heimberg et al., employing in-vitro rat liver perfusion, demonstrated that the addition of epinephrine to the perfusate significantly increased the rate of hepatic ketogenesis ($p < 0.02$).[5] Finally, Exton et al. examined the ketogenic effect of epinephrine in perfused livers removed from non-diabetic rats.[6] In their studies, the mean ± S.E.M. hepatic ketone-body production rate of the control and epinephrine-(1×10^{-7} M)-stimulated liver was 10.6 ± 0.7 and 12.6 ± 1.0 μmol/100 gm.-rat liver per hour, respectively, but no statistical comparisons were reported. Thirdly, norepinephrine may elevate plasma ketone bodies by inhibiting peripheral ketone body utilization. Although no data are available directly examining this issue, it is of interest that catecholamines have been shown to exert a peripheral inhibitory action on glucose uptake by skeletal muscle in vitro.[29]

In our study, norepinephrine infusion resulted in the simultaneous elevation of circulating glucagon concentration. This observation has not previously been made for physiologic elevations in plasma norepinephrine in vivo, although Gerich et al. have demonstrated that physiologic elevations in plasma epinephrine do stimulate endogenous glucagon secretion.[30] In-vitro norepinephrine stimulation of pancreatic glucagon has been observed.[31] Since a physiologic elevation of plasma glucagon following exogenous glucagon infusion in insulin-dependent diabetic subjects results in an elevation of plasma ketone bodies[10] independent of FFA mobilization, this mechanism may also participate in the hyperketonemia following norepinephrine infusion. However, this mechanism cannot be unequivocally implicated in the present study because the levels of plasma glucagon achieved in the current studies were significantly lower (less than 150 pg./ml.) than achieved in the glucagon-infusion studies (greater than 250 pg./ml.). In addition, Silverberg et al.[21] have observed a rise in plasma ketone bodies following norepinephrine infusion without a concurrent rise in plasma glucagon concentration. Other counterregulatory hormones, in-

cluding growth hormone and cortisol elevation, may also result in increased plasma ketone-body concentration.[32,33] However, no significant difference in growth hormone or cortisol concentration was observed between the control-heparin and norepinephrine-infusion studies. Thus, of the three counterregulatory hormones monitored, only glucagon may potentially participate in the hyperketonemic response of norepinephrine infusion.

Our study suggests that norepinephrine is a hyperketonemic and hyperglycemic hormone in insulin-dependent diabetic subjects. Its ketonemic activity results, in part, from augmentation of plasma free fatty acid substrate availability. However, our study demonstrates for the first time in man that norepinephrine has ketogenic activity in addition to its ability to augment lipolysis and increase substrate availability for hepatic ketogenesis. This additional ketogenic activity may be a direct catecholamine effect on hepatic ketogenesis and/or be secondary to catecholamine stimulation of endogenous secretion of glucagon. In any event, since diabetic ketoacidosis is characterized by tenfold elevations in plasma norepinephrine concentration,[1] it is attractive to speculate that the hyperketonemia of this pathologic state may result, at least in part, from catecholamine-induced ketosis.

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