The Role of “Diabetogenic” Hormones on Carbohydrate and Lipid Metabolism Following Oral Glucose Loading in Insulin Dependent Diabetics: Effects of Acute Hormone Administration

P. Bratusch-Marrain, W. Waldhäusl, B. Grubeck-Loebenstern, A. Korn, H. Vierhapper and P. Nowotny

Division of Clinical Endocrinology and Diabetes Mellitus, I. Medizinische Universitätsklinik, Vienna, Austria

Summary. To evaluate the relative role of “diabetogenic” hormones as insulin antagonists in severe derangements of diabetic control, glucagon, cortisol, growth hormone and adrenaline were administered by continuous intravenous infusion, separately and in combination, to ketosis-prone insulin-dependent diabetics ($n = 11$). The amount of insulin required for the assimilation of a 50 g glucose load during the various hormone infusions was determined by means of an automated glucose-controlled insulin infusion system and used as an index of insulin effectiveness. Raising plasma hormone concentrations acutely into the range seen in severe diabetic states (glucagon 517 ± 70 pg/ml; cortisol 32 ± 3 μ g/dl; growth hormone 14 ± 3 ng/ml) did not alter significantly blood glucose profile and insulin requirement (control 11.3 ± 1.1 U; glucagon 11.6 ± 2.0 U; cortisol 11.1 ± 0.4 U; growth hormone 12.9 ± 1.4 U), except for adrenaline (plasma level 550 ± 192 pg/ml), which caused a marked rise in blood glucose levels and a threefold increase in insulin demand (31.1 ± 3.7 U). Combined infusion of all hormones did not potentiate significantly the latter effect (38.3 ± 4.7 U). The effectiveness of metabolic control by insulin was assessed by a marked decrease in plasma non-esterified free fatty acids and ketone bodies upon its administration after glucose ingestion in all groups studied. It is concluded that from the hormones investigated within this study adrenaline exerts the strongest diabetogenic action during its short term administration followed by that of growth hormone. Whereas it may well be that over-insulinization of the patients by the glucose controlled insulin infusion system has overcome and disguised the smaller diabetogenic effects of cortisol and glucagon.

Key words: Diabetes mellitus, counter-regulatory hormones, glucagon, cortisol, growth hormone, adrenaline, insulin, non-esterified fatty acids, ketone bodies.

Excess secretion of insulin-counteracting hormones is claimed to be important in the metabolic changes and insulin resistance in diabetic ketoacidosis [1, 2]. The observations in severe derangements of diabetic control include elevated plasma levels of glucagon [3], cortisol [4], growth hormone [5, 6], and catecholamines [7, 8]. The hierarchy of their pathogenetic significance, however, remains to be established. Hyperglycaemia, decreased glucose tolerance and insulin resistance have been demonstrated under certain circumstances after exogenous administration of these hormones [9–12]. Furthermore, the above mentioned counter-regulatory hormones are known to exert lipolytic and ketogenic activity when elevated to high physiological concentrations in insulin deficient diabetic man [12–16]. The delay in the development of ketoacidosis in insulin-withdrawn diabetics by either somatostatin-induced suppression of growth hormone and glucagon [17] or following pituitary ablation [1] serves as further support for implicating these hormones as pathogenic factors of deranged metabolic control. In addition, circulatory levels of the same hormones increase in response to insulin-induced hypoglycaemia [7, 18–20] raising the question of their relative impact as insulin antagonists in this condition.

The present study was therefore undertaken to assess the effect of acutely increasing circulating levels of insulin-opposing hormones to levels reported in severe derangements of diabetic control and insulin-induced hypoglycaemia by examining their impact upon glucose disposal. For this purpose the amount of insulin required to assimilate an oral glucose load (50 g) was estimated by means of a glucose controlled insulin infusion system (artificial endocrine pancreas) [21] in insulin-dependent diabetics, who received short-term infusions of exogenous glucagon, cortisol, growth hormone and adrenaline. Our results emphasize the role of adrenaline as the one exerting the most pronounced insulin-opposing action.

Table 1. Plasma concentrations of glucagon, growth hormone, cortisol and adrenaline before (–120 min) and during constant IV infusion of the respective hormones. Zero-time refers to the oral glucose load (50 g). Hormone infusion was started at –120 min

Plasma concentrations	No. of patients	Time (min) –120	–15	0	+60	+120	+180
Glucagon (pg/ml)	6	103±25	474±35	536±77	526±89	568±83	523±82
Growth hormone (low-dose, ng/ml)	3	4.0±1.6	15.0± 5.3	13.6± 4.1	12.7± 3.2	15.2± 3.4	15.6± 1.6
Growth hormone (high-dose, ng/ml)	6	5.8±5.1	64.5±10.1	67.4± 9.1	65.8±14.8	64.4±11.1	64.4± 9.6
Cortisol (low-dose, µg/dl)	6	5.9±0.7	19.6± 2.6	19.2± 2.5	20.4± 1.5	20.3± 2.9	24.8± 2.0
Cortisol (high-dose, µg/dl)	3	11.9±2.2	28.2± 3.4	30.8± 5.2	34.0± 4.8	34.6± 5.2	34.6± 1.6
Adrenaline (pg/ml)	6	73±10	520±190	550±192	470±195	472±155	608±258

Mean values ± SEM are given

Patients and Methods

Patients

Eleven insulin-dependent male diabetics (aged 21–34 years) who were characterized by failure of C-peptide release upon arginine stimulation (30 g arginine hydrochloride IV/30 min) as well as minimal plasma insulin binding capacity of less than 5 µg/l, participated in the study. Each had been receiving insulin for 6.4±1.7 years (range: 6 months – 20 years) and was within 6% of ideal body weight (Metropolitan Life Insurance Table, 1959 [22]). None was taking any medication other than insulin at the time of the study. Subcutaneous administration of intermediate-acting insulin was withheld for at least 15 h before the study. Insulin administration, caloric intake and distribution were kept constant for each subject between the tests. The investigation was approved by the Research Committee of the hospital. Patients were informed of the nature and possible risks of the study before giving their voluntary consent to participate. None of them experienced any untoward side-effects during any of the procedures.

Study Protocol

Studies were performed during feed-back control of hyperglycaemia with an automated glucose-controlled insulin infusion system (Biostator; Miles, Ulm, FRG). Blood glucose (BG) concentrations were tabulated each minute and accuracy checked every 30 min by a glucose analyzer employing the glucose oxidase method ("Reflomat", Boehringer-Mannheim, FRG). Control algorithms were identical for all studies and were chosen to stabilize BG at 5.5 mmol/l with a basal insulin infusion rate of 15 mU/min (KR 165, KF 45, QI 30). Maximal insulin delivery rate was limited to 250 mU/min to avoid unphysiologically high plasma levels with resultant hypoglycaemia, as no glucose infusion was allowed at any time. The glass insulin reservoir contained 120 U of soluble insulin (Insulin "Hoechst" CS) added to 500 ml isotonic saline (0.5% human albumin). Studies with inappropriate BG control due to technical difficulties, such as clogging of the double lumen catheter or failure of the glucose oxidase membrane, were omitted from consideration.

Each study began at 0600 h after an overnight fast and BG was brought to 8 mmol/l by glucose-controlled insulin infusion before continuous infusion of one or more "diabetogenic" hormones was initiated. Consecutively, an initial 2 h period was allowed to reach a steady state of the respective hormone(s) and to achieve and maintain BG at 5–6 mmol/l. Thereafter a load of 50 g glucose monohydrate (Glucotest, Boehringer Mannheim, FRG) cor-

responding to 50 g glucose in 110 ml of water was administered orally and followed by 110 ml of tap water. After glucose loading, BG and insulin requirement were determined for at least 3 h until BG fell to pretest levels. Blood samples for measurements of non-esterified plasma free fatty acids (NEFA), acetoacetate, beta-hydroxy-butyrate and hormone concentrations were obtained at 30 min intervals.

Hormone Infusions

Each patient served as his own control (saline infusion) and participated in at least three to six hormone infusion studies, which were performed in a random sequence at least 5 days apart. Four different hormones, subsequently referred to as "counter-regulatory" or "diabetogenic", were infused: glucagon (Eli Lilly, Indianapolis, USA; 360 ng · kg body weight⁻¹ · h⁻¹; *n* = 6); growth hormone (Crescormone R, AB Kabi, Stockholm, Sweden; low dose, 2 µg · kg⁻¹ · h⁻¹, *n* = 3; high dose, 10 µg · kg⁻¹ · h⁻¹, *n* = 6); cortisol (Hydrocortison R, Hoechst, Frankfurt, FRG; low dose, 6 mg/h, *n* = 6; high dose, 10 mg/h, *n* = 3); adrenaline (Suprarenin R, Hoechst, Frankfurt, FRG; 180 µg/h, *n* = 6). In addition, a "cocktail" consisting of glucagon (360 ng · kg⁻¹ · h⁻¹), growth hormone (2 µg · kg⁻¹ · h⁻¹), cortisol (10 mg/h) and adrenaline (180 µg/h) was given to five patients to mimic hormone concentrations in severe derangements of diabetic control [14]. Each hormone was dissolved in saline containing 1.5 g human albumin/100 ml. Constant infusion at appropriate rates (6 ml/h for glucagon, growth hormone and cortisol; and 60 ml/h for adrenaline) was achieved by a perfusion pump (Braun – Melsungen, FRG).

Analytical Methods

Methods and standards used for the estimation of immunoreactive glucagon (IRG), C-peptide, growth hormone, cortisol and of insulin binding capacity have been described previously [8, 23, 24]. Adrenaline and noradrenaline were estimated radio-enzymatically [25]. Plasma concentrations of NEFA were determined by the modification of Trout et al. [26]. Beta-hydroxybutyrate and acetoacetate were estimated enzymatically [27, 28]. Total ketone body concentration refers to the sum of butyrate and acetoacetate concentrations.

Statistics

Mean values (± SEM) are indicated in text, tables and figures. The paired Student's *t*-test was employed for statistical analysis.

Fig. 1. Effect of an oral glucose load (oGTT, 50 g) on the mean blood glucose concentration and the insulin infusion rate administered by an automated glucose-controlled insulin infusion system during saline (—, $n = 11$) and adrenaline infusion (---, $n = 6$) in insulin dependent diabetics. The mean profiles obtained during the infusion of the other hormones (glucagon, growth hormone and cortisol) lay within the range of the values (mean $\pm$ SEM) in the saline study as indicated by the shaded area

Results

Hormone Concentrations

The plasma concentrations of glucagon, growth hormone, cortisol, and adrenaline obtained by constant IV infusion of the respective single hormones were in a steady state throughout the observation period and well within the range observed in severe derangements of diabetic control (Table 1). Plasma concentrations of the hormones other than those infused remained within the range observed in the control study; except for erratic growth hormone peaks twofold above basal that were recorded in the control as well as during the various hormone infusion studies. They were unrelated to acute changes in blood glucose levels. Mean plasma noradrenaline

Fig. 2. Effect of continuous IV administration of "diabetogenic" hormones on insulin requirement following an oral glucose load (50 g) in insulin dependent diabetics. Mean $\pm$ SEM (n). Asterisks indicate significant difference when compared with the control value (* $p < 0.05$, ** $p < 0.0005$)

concentrations at 0-time were 210 ± 19 pg/ml and did not change during the various hormone infusions. Plasma hormone concentrations observed during infusion of the "cocktail" of diabetogenic hormones were in the same range as observed after infusion of the respective individual hormones. As all patients were chosen on the basis of a negative C-peptide response upon IV arginine, no increase in C-peptide levels was observed during any of the studies.

Blood Glucose Profiling

With the exception of the adrenaline and "hormone cocktail" study, the blood glucose profiles recorded by the artificial endocrine pancreas were nearly identical during the administration of the various hormones. Mean BG concentrations and insulin infusion rates for the saline and adrenaline infusion study were calculated at 5 min intervals and are presented in Figure 1. The mean BG profiles during the infusion of glucagon, growth hormone and cortisol lay within the $\pm$ SEM range of the saline study. Calculating the area under the curve describing BG concentrations in percentage of those during the control study (= 100%) the following relations were found for the infusion of: glucagon, $95 \pm 5\%$; low-dose growth hormone, $97 \pm 3\%$; high-dose growth hormone, $112 \pm 11\%$; low-dose cortisol, $100 \pm 6\%$; high-dose cortisol, $104 \pm 6\%$. During the infusion of adrenaline a more marked increase and protracted decrease in BG levels was seen (adrenaline, $152 \pm 13\%$, $p < 0.0025$; "cocktail", $159 \pm 16\%$, $p < 0.0025$ versus control).

Table 2. Effect of oral glucose loading (50 g at 0-time) during saline, glucagon, growth hormone, cortisol, adrenaline and combined hormone ("cocktail") infusion upon plasma concentrations of non-esterified free fatty acids and ketone bodies in insulin dependent diabetics controlled by the artificial endocrine pancreas.

	No. of patients	Time min -120	0	+30	+60	+90	+120	+150	+180
Non-esterified free fatty acids (mmol/l)									
Saline	11	0.51±0.15	0.47±0.05	0.41±0.07	0.27±0.05 ^a	0.23±0.05 ^c	0.25±0.05 ^b	0.37±0.11	0.46±0.09
Glucagon	6	0.33±0.08	0.34±0.08	0.40±0.11	0.25±0.06	0.21±0.06	0.23±0.07	0.27±0.05	0.56±0.11
Growth hormone (low-dose)	3	0.38±0.02	0.62±0.28	0.57±0.20	0.42±0.05	0.43±0.08	0.47±0.09	0.54±0.15	0.60±0.23
Growth hormone (high-dose)	6	0.24±0.07	0.70±0.14	0.59±0.08	0.27±0.04 ^b	0.23±0.05 ^c	0.29±0.05 ^b	0.37±0.07 ^b	0.53±0.11
Cortisol (low-dose)	6	0.44±0.18	0.49±0.13	0.60±0.12	0.46±0.15	0.30±0.07 ^a	0.36±0.11 ^a	0.59±0.23	0.61±0.21
Cortisol (high-dose)	3	0.34±0.08	0.51±0.10	0.48±0.12	0.38±0.11	0.30±0.07 ^a	0.27±0.05 ^a	0.25±0.02 ^a	0.28±0.03 ^a
Adrenaline	6	0.30±0.11	0.99±0.09	0.91±0.13	0.43±0.16 ^c	0.25±0.07 ^d	0.25±0.10 ^d	0.20±0.09 ^d	0.26±0.11 ^d
"Cocktail"	5	0.29±0.06	0.73±0.19	0.71±0.10	0.55±0.08	0.57±0.10	0.61±0.08	0.62±0.08	0.61±0.01
Ketone bodies (mmol/l)									
Saline	11	0.47±0.06	0.47±0.03	0.51±0.03	0.46±0.05	0.40±0.04 ^b	0.39±0.03 ^c	0.38±0.03 ^c	0.45±0.03
Glucagon	6	0.39±0.07	0.41±0.05	0.48±0.06	0.44±0.05	0.38±0.05	0.35±0.04 ^a	0.39±0.07	0.37±0.06
Growth hormone (low-dose)	3	0.70±0.24	0.71±0.24	0.86±0.19	0.69±0.10	0.59±0.09	0.57±0.10	0.59±0.05	0.60±0.08
Growth hormone (high-dose)	6	0.48±0.05	0.57±0.08	0.62±0.08	0.51±0.07	0.43±0.05 ^a	0.42±0.03 ^a	0.42±0.04 ^a	0.49±0.05
Cortisol, low-dose	6	0.60±0.18	0.61±0.20	0.68±0.22	0.62±0.13	0.50±0.04	0.51±0.08	0.56±0.11	0.64±0.16
Cortisol, high-dose	3	0.37±0.02	0.52±0.07	0.64±0.18	0.57±0.16	0.51±0.08	0.46±0.09	0.46±0.05	0.42±0.04
Adrenaline	6	0.55±0.12	0.90±0.21	0.95±0.19	0.79±0.16	0.57±0.09 ^a	0.52±0.04 ^a	0.46±0.04 ^a	0.45±0.06 ^a
"Cocktail"	5	0.71±0.13	1.12±0.40	1.14±0.38	1.05±0.30	0.99±0.31	0.96±0.22	0.95±0.20	1.00±0.20

Mean values ± SEM. *p*-values indicate significant difference from the value obtained before the oral glucose load (0-time): ^a *p* < 0.05, ^b *p* < 0.01, ^c *p* < 0.005, ^d *p* < 0.0005.

Insulin Requirement

As with the BG profile the pattern of insulin administration during glucagon, growth hormone and cortisol infusion was similar to that in the control study exhibiting a prompt increase following glucose ingestion and a consecutive decrease with falling BG levels. Whereas in the studies employing adrenaline infusion, insulin at maximal or near maximal rate was administered for at least 2 h to combat severe hyperglycaemia. As shown in Figure 2, the amount of insulin infused during the 3 h observation period following glucose loading to achieve normalization of BG concentrations was 11.3 ± 1.1 U in the control study. Similar doses of insulin were required when glucagon (11.6 ± 2.0 U), cortisol (low-dose, 12.8 ± 3.3 U; high-dose 11.1 ± 0.4 U) or low-dose growth hormone (12.9 ± 1.4 U) were administered. During high-dose growth hormone infusion a 50% increase in insulin requirement (17.8 ± 4.4 U; *p* versus control < 0.05) was necessary to obtain comparable BG profiling. Raising plasma adrenaline concentrations a more marked augmentation of insulin requirement to 31.1 ± 3.7 U was observed (*p* versus control < 0.0005). Compared with the latter study a small further, albeit not significant increase was found when the hormone "cocktail" was administered (38.3 ± 4.7 U).

Non-esterified Free Fatty Acids and Ketone Bodies (Table 2)

Before the initiation of hormone infusion (-120 min) mean plasma NEFA concentration was 0.35 ± 0.04 mmol/l. In the following 2 h period, no significant change in NEFA was seen in the control study and during glucagon, low dose growth hormone, and cortisol infusion, whereas a two to threefold rise was observed upon high-dose growth hormone (*p* < 0.0005), adrenaline (*p* < 0.0005) and hormone "cocktail" (*p* < 0.05) administration. Following glucose loading (0-time) NEFA fell consistently in parallel with ketone body concentration when compared with values obtained at 0-time in all subjects during the first 60–120 min when insulin administration was maximal. Thereafter, plasma levels of both metabolites increased towards the end of the observation period in the studies with saline, glucagon, growth hormone or cortisol at the time insulin administration approached basal rate. Whereas, in the adrenaline study plasma concentrations of NEFA and ketone bodies remained suppressed with ongoing elevated insulin infusion rate. When the hormone cocktail was infused plasma NEFA and

ketone bodies exhibited a less pronounced fall compared with the adrenaline study and remained elevated throughout the study thereafter.

Discussion

This study demonstrates that in insulin-dependent diabetics plasma concentrations of glucagon, cortisol, and growth hormone elevated acutely to the range usually observed in severe derangements of diabetic control [8] do not materially affect glucose tolerance as judged by the amount of insulin required to utilize an oral glucose load. In contrast, increased amounts of insulin were required in the presence of elevated adrenaline concentrations, which thus seem to play a most important role in the decrease of insulin action on carbohydrate metabolism. This effect of elevated plasma adrenaline as well as the well known suppression of endogenous insulin release by adrenaline [29] may explain the known positive relationship between stress of various causes and the onset of deranged control of the diabetic state [30]. Thus even emotional factors, which are accompanied by catecholamine release, may aggravate the metabolic state of diabetic patients who are otherwise well controlled by insulin therapy [31].

In relation to glucagon, this study is in line with the concept that as long as insulin is available to maintain blood glucose concentration within the normal range, elevated plasma glucagon concentrations do not alter glucose tolerance neither acutely nor after long-term experimental exposure [32–34]. However, our study does not exclude the possibility that in patients with insulin supply insufficient for strict euglycaemic control, glucagon may be a potent glucogenic hormone and may cause deterioration of glucose tolerance [9]. In the case of growth hormone, only high-dose hormone infusion mimicking plasma concentrations in the range observed in acromegalic patients and only rarely in severe diabetic ketoacidosis [5] led to a 60% increase in insulin requirement; whereas growth hormone concentrations of 10–20 ng/ml as usually seen in poorly controlled diabetics [35], and in many of the patients with severe diabetic ketoacidosis, did not influence insulin requirement. Also, cortisol infused acutely at two different doses was without any demonstrable effect on glucose tolerance. As the hormone's individual action on carbohydrate tolerance may be enhanced or antagonized by the concomitant hypersecretion of the other counter-regulatory hormones under discussion, their combined effect was studied by the infusion of a hormone cocktail thereby imitating the hormone profile seen in a decompen-

sated state of diabetes mellitus. The observed lack of any major potentiating effect of combined hormone infusion, as compared with adrenaline alone, underlines again a primacy of the latter hormone in the pathogenesis of acute insulin resistance. This observation is in part in contrast to the reported enhancement of the hyperglycaemic action of adrenaline by simultaneous elevation of cortisol [36].

Since the patients' insulin requirement was used as a measure of potential insulin resistance, serum levels of free insulin were not determined. However, high serum concentrations of free insulin are to be anticipated as most diabetic subjects were receiving an insulin infusion of 100 mU/min, and some even of 200 mU/min. Thus the insulin dose administered by the glucose controlled insulin infusion system for assimilation of 50 g of glucose was considerably greater than the 6.8 ± 1.4 U (SEM) of insulin released by healthy man after ingestion of the same glucose load [37]. This implies that the induced over-insulinization of the diabetic patients might have reduced any expected effects of the weaker counter-regulatory hormones, glucagon and cortisol on glucose assimilation. As to the absence of any diabetogenic action of glucagon, it has to be kept in mind that although peripheral plasma glucagon concentrations were increased to values seen in ketoacidosis, the portal concentrations may have been considerably lower in the present study as compared with severe derangements of carbohydrate metabolism.

In this context it has to be emphasized that the present studies were conducted as short-term experiments with exogenous hormone infusion preceding glucose tolerance testing by 2 h only. Thus the results obtained are not at variance with the concept of tissue resistance to insulin action in states of chronic diabetogenic hormone excess, such as in acromegaly [38] and in Cushing's syndrome [39]. A possible influence of long-term exposure to insulin opposing hormones may be anticipated as a time-dependence has recently been demonstrated for growth hormone on lipid metabolism in insulin-withdrawn diabetics by Schade and Eaton [15]. Further studies with hormone administration over extended periods of time are required to estimate their late-term effects on glucose tolerance.

The acute release of diabetogenic hormones in response to insulin-induced hypoglycaemia [10, 19, 20, 40] has been presumed to contribute also to insulin resistance and impaired glucose tolerance with subsequent hyperglycaemia ("Somogyi effect") [41]. On the basis of the present results, it would seem that only catecholamines possess the potency to normalize rapidly blood glucose concentration after insulin-induced hypoglycaemia, whereas glucagon,

cortisol, and growth hormone seem to be of no major relevance to the acute restoration of glucose homeostasis. This impact of adrenergic mechanisms in the initiation of the counter-regulatory response to insulin-induced hypoglycaemia in man has also been underlined by the observation that of all the hormones studied only the increment in plasma catecholamines preceded the increase in hepatic glucose production [42].

In addition to the insulin counteracting effects of glucagon, growth hormone, cortisol and adrenaline in relation to carbohydrate metabolism, the impact of these hormones upon NEFA and ketone body metabolism has also been studied. In insulin-deficient man the pathogenic significance of these hormones has been demonstrated by their lipolytic and ketogenic activity when given in physiological concentrations [12–16, 43], and by the amelioration of hyperketonaemia with pharmacological blockade of individual counter-regulatory hormones [2, 43]. In our control experiments, following ingestion of glucose and adequate insulin administration, NEFA and ketone bodies decreased initially but increased with termination of intestinal glucose absorption and subsequent reduction of insulin administration [44]. This pattern of NEFA and ketone bodies was also seen during glucagon, growth hormone and cortisol administration, implying that the patients were sufficiently insulinized to obviate the lipolytic effect of these hormones. These studies are in keeping with the results described by Pozefsky et al. [45], who were unable to demonstrate any effect of raised glucagon concentrations on lipid metabolism in forearm perfusion studies in healthy man. In insulin-deficient diabetic man, however, glucagon is ketogenic at physiological levels and is capable of stimulating both lipolysis and ketogenesis at pharmacological levels; an effect that is easily antagonized by appropriate insulin availability [46]. Similarly, pathophysiological levels of growth hormone can augment lipolysis and ketone body production in insulin-deficient man, but these actions are not apparent in the presence of physiological levels of insulin [15, 43]. A demonstrable effect of cortisol on NEFA metabolism may not have occurred in our short term studies in contrast to the hyperketonaemia which has been demonstrated after chronic steroid administration [14].

In the adrenaline study, NEFA and ketone bodies after an initial decrease remained low as long as insulin was being administered at high rates in order to maintain euglycaemia. In the "cocktail" study plasma NEFA and ketone body concentrations remained elevated throughout despite ongoing insulin administration. Thus it is likely that the combined hormone infusion mimicking the hormonal profile in a

decompensated state of diabetes mellitus enhances lipolysis and ketogenesis more markedly than adrenaline alone, whereas there is only a small alteration in glucose tolerance.

In summary, in insulin-dependent diabetic patients plasma concentrations of "diabetogenic" hormones elevated acutely to levels seen in severe derangements of diabetic control do not appear to exert a major influence on insulin effectiveness and insulin requirement, except for adrenaline. Furthermore, an important role of adrenaline on carbohydrate metabolism in the counter-regulatory response to hypoglycaemia has been suggested. Our findings may also explain the fact well known to the practicing physician that loss of control in diabetic patients following stress of various causes may be associated with increased catecholamine release.

Acknowledgements. Skilful technical assistance was provided by Mrs. A. Hofer, Mrs. E. Nowotny and Miss B. Neuhuber. We also wish to express our thanks to Miss V. Kaufmann, Mr. R. Stögerer and Mr. K. Liener for their invaluable help in the care and control of the artificial endocrine pancreas. This study was supported, in part, by a grant (No. 3875) to Dr. W. Waldhäusl of the "Fonds zur Förderung der wissenschaftlichen Forschung Österreichs" and Hoechst Austria.

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Received: 2 January 1981
and in revised form: 30 March 1981

Dr. P. Bratusch-Marrain
I. Medizinische Universitätsklinik
Lazarettgasse 14
A-1090 Vienna, Austria