Variation in the Disappearance of Unlabeled Insulin from Plasma

Studies with Portal and Peripheral Infusions

KARL-GÖRAN TRANBERG AND JAN THORELL

SUMMARY

One hundred and thirty brief infusions of unlabeled insulin were given to 75 unanesthetized nondiabetic human beings. The patients were examined (1) by different doses of insulin (5–50 mU/kg), (2) by intraportal and peripheral infusion, (3) in the morning and in the afternoon, and (4) during normoglycemia and moderate, steady hyperglycemia. After intraportal infusion of insulin, the non-steady state plasma clearance rate (ml min^{-1} kg^{-1}) was lower the larger the dose (decreased about 50% by a 10-fold increase in insulin dose) and lower at hyper- than at normoglycemia (decreased about 30% after small insulin doses). It was also lower the higher the relative body weight, but this correlation was weak. After peripheral insulin infusion, none of the above relationships was demonstrated. Regardless of the route of insulin infusion, plasma clearance rate did not vary with fasting plasma insulin concentration, time of day, insulin sensitivity, or glucose tolerance. We conclude that the liver modifies the distribution and removal of pancreatically released insulin in response to acute increases in insulin or glucose. Otherwise the plasma clearance rate of insulin showed a notable lack of relationships with common indexes of metabolism and with insulin action. DIABETES 28:846–851, September 1979.

The current concept of insulin receptor regulation by insulin[1] has revived the interest in factors related to insulin metabolism and its coupling with insulin action. Also, it has brought into focus the question to what extent the plasma insulin concentration is determined by the rate of disappearance. But studies in vivo are few and the results are not unanimous.[2–6] Furthermore, in human beings, disappearance of insulin entering the circulation via the physiologic portal route has been studied only with labeled insulin during anesthesia.[7]

Having the opportunity to investigate patients on whom portal catheterization was performed for possible liver metastases,[8] we studied the disappearance of insulin from plasma after a brief infusion of insulin into the portal vein. In a previous report,[9] we analyzed the kinetics of insulin removal from plasma. This paper describes how the clearance of insulin is related to variables such as plasma insulin, blood glucose, insulin sensitivity, glucose tolerance, relative body weight, and time of day. The results were also compared with those obtained after infusion of insulin into a peripheral vein in order to estimate the role played by the liver.

MATERIALS AND METHODS

Subjects. The materials consisted of surgical ward patients with normal fasting blood glucose concentrations. None had previous endocrine disease, and none was receiving any drug known to disturb insulin or carbohydrate metabolism. Body weights ranged from 50 to 97 kg and from 86 to 141% of the ideal (tables of Metropolitan Life Insurance Company). The results of standard liver and kidney laboratory tests were normal in all.

Intraportal infusions of insulin were given to 58 patients with a transumbilical portal catheter.[8] In addition, 39 of these 58 patients received peripheral insulin infusions, as did 17 other patients. Since the experimental procedure varied with respect to the route of insulin infusion, time of day, and glucose concentration, the clinical characteristics of each study group are summarized in Table 1. Most patients with a portal catheter were to be, or had been, treated for carcinoma of the colon, whereas patients receiving only peripheral infusions of insulin had a variety of diagnoses, mostly inguinal hernia. There was otherwise no difference in basic clinical or laboratory data between the study groups or between patients with and without a portal catheter (Table 1). Patients with portal catheters were examined for liver metastases by means of portography,[8] liver scintigraphy, and subsequent laparotomy. Only patients without demon-

From the Department of Surgery, University of Lund, and the Department of Nuclear Medicine, General Hospital, Malmö, Sweden.
Address reprint requests to Dr. K.-G. Tranberg, Department of Surgery, University of Lund, S-221 85 Lund, Sweden.
Received for publication 15 January 1979 and in revised form 23 May 1979.

TABLE 1
Clinical characteristics of each study group

Route of insulin infusion	Time of day	Glucose infusion	No. of subjects*	Sex (M/F)	Age (yr)	Relative weight (% of ideal)	Fasting blood glucose (mmol/L)	Fasting plasma FFA (μmol/L)	Fasting plasma insulin (μU/ml)	k_G (%/min)	Diagnosis		
											Neoplasm†	Inguinal hernia	Miscellaneous‡
Portal	0800	−	32 (36)	20/12	63.0 ± 8.1	112 ± 12	4.32 ± 0.55	388 ± 90	12.0 (5.6–20.0)	0.95 ± 0.25	28 (4)		
	0800	+	16 (16)	7/9	67.6 ± 5.5	111 ± 11	4.41 ± 0.34	358 ± 100	12.0 (8.0–16.0)	1.13 ± 0.27	13 (2)		1
	1400	−	10 (10)	6/4	61.4 ± 7.1	109 ± 10	3.90 ± 0.48	490 ± 69	3.0 (1.2–7.0)	0.89 ± 0.15	10		
Peripheral	0800	−	41 (53)	29/12	62.0 ± 10.7	111 ± 12	4.22 ± 0.51	361 ± 106	10.0 (5.0–17.0)	0.95 ± 0.27	20 (4)	7	10
(Peripheral only			17 (27)	14/3	60.1 ± 13.1	109 ± 11	4.26 ± 0.42	395 ± 157	10.0 (4.6–21.0)	1.07 ± 0.25		7	10)
	0800	+	15 (15)	7/8	67.3 ± 5.6	111 ± 11	4.52 ± 0.59	369 ± 124	11.0 (7.0–13.8)	1.12 ± 0.28	12 (2)		1

The plasma insulin values are medians and 20th and 80th percentiles; otherwise, the values are means ± SD.

* Numbers of insulin infusions are given within parentheses.

† Neoplasm of the colon or, when in parentheses, of the urinary tract.

‡ Malignant disease, 4; nephrolithiasis, 3; sigmoiditis, 3; gastritis, 1; crural varices, 1.

strable metastases or portal-systemic shunting were included. No study was performed within 6 mo after major operation. In six patients undergoing inguinal herniorraphy, studies were performed also 3 days postoperatively. The results of these postoperative studies were excluded from the rest and are given separately.

The portal catheter had been inserted, under general anesthesia, 2 days before portography and 3 days before the experimental studies. The day after catheterization, the patients resumed their preoperative routine, walked about freely in the ward, and ate an ordinary hospital diet. The portal catheter was kept patent by continuous infusion of 5000 IU of heparin in 1000 ml of saline each day.

The investigations were performed in conformity with the principles laid down in the Declaration of Helsinki. Verbal informed consent was obtained from all participants.

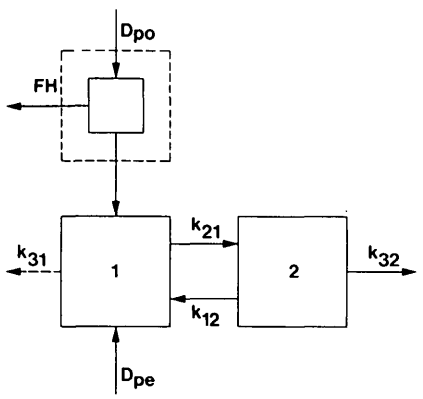
Experimental procedures are described in detail elsewhere.[9] The studies were begun after an overnight fast, 1 h after discontinuation of the portal infusion of heparin and cannulation of a radial artery for blood sampling. When the patient was to receive a peripheral infusion, a contralateral cubital vein was also catheterized. When glucose was infused, it was given via the portal catheter throughout the experiments, and then the pretest period was extended 90 (during infusion of 80 mg kg^{-1} h^{-1}) or 120 (during infusion of 200 mg kg^{-1} h^{-1}) min to ensure steady levels of glucose and insulin before the infusion of insulin.[9] The infusions of glucose raised the arterial blood glucose concentrations by 0.89 ± 0.46 and 2.32 ± 0.82 mmol/L, respectively, and the plasma insulin concentrations by 4.0 ± 6.4 and 21.6 ± 21.2 μU/ml, respectively. During glucose infusion, portal blood glucose concentration was about 0.4 and 1 mmol/L higher than that in arterial blood. Unless otherwise stated, studies were begun in the morning. In 10 patients, fasting was prolonged to 1400 h before the studies began. In patients examined twice, the second study was performed 1 day after the first.

Insulin Actrapid (monocomponent porcine insulin at neutral pH; Novo A/S, Copenhagen) was infused for 2.5 min, and samples were taken at frequent intervals from a radial artery during the next hour. An intravenous glucose tolerance test (IVGTT) was begun 60 min after start of the insulin infusion by giving 25 g of glucose in 100 ml of water into a peripheral vein during 2 min. Arterial blood for glucose determination was sampled 72, 80, 90, 110, and 120 min after the beginning of the insulin infusion (time 0).

Analytic methods. Sampling tubes contained EDTA. Blood glucose was measured in triplicate with a glucose oxidase method,[10] the within-assay coefficient of variation being 2.5% at a level of 3.70 mmol/L. Plasma was rapidly separated and stored at −20 °C until determination of total insulin immunoreactivity[11] and FFA.[12] Details of the insulin assay are presented elsewhere.[9] The within-assay coefficient of variation for FFA was 2%.

Calculations. The disappearance of insulin from plasma was previously analyzed in detail with emphasis on the computations, the assumptions, and the limitations of the equations employed.[9] Plasma clearance rate, PCR (ml min^{-1} kg^{-1}), was calculated as the dose divided by the area of the incremental plasma insulin concentrations, i.e., as PCR = $D/\int_0^\infty IRI\ (t)\ dt$, where D (μU/kg) is the dose of insulin and IRI (μU/ml) is the immunoreactive insulin concentration above the pretest baseline in arterial plasma.* Since this

FIGURE 1. Compartmental model for portal and peripheral infusion (D_{po}, portal dose; D_{pe}, peripheral dose).[9] For portal infusion, the first pass fractional hepatic uptake is designated FH. After the first liver passage, (1-FH)D_{po} (the posthepatic dose) thus reaches the systemic circulation. The hepatic removal of posthepatic (recirculating), and peripherally administered, molecules is lumped together with the removal in peripheral tissues. For molecules entering the systemic circulation, the flow between intravascular (1) and extravascular (2) compartments has rate constants k_{21} and k_{12} and the irreversible loss has rate constant k_{32} (or k_{31}).



* Abbreviations used in this paper: PCR, plasma clearance rate; k_{el}, net fractional disappearance rate from systemic circulation; APV, apparent plasma volume. The subscripts po and pe denote, respectively, the portal and peripheral routes of infusion.

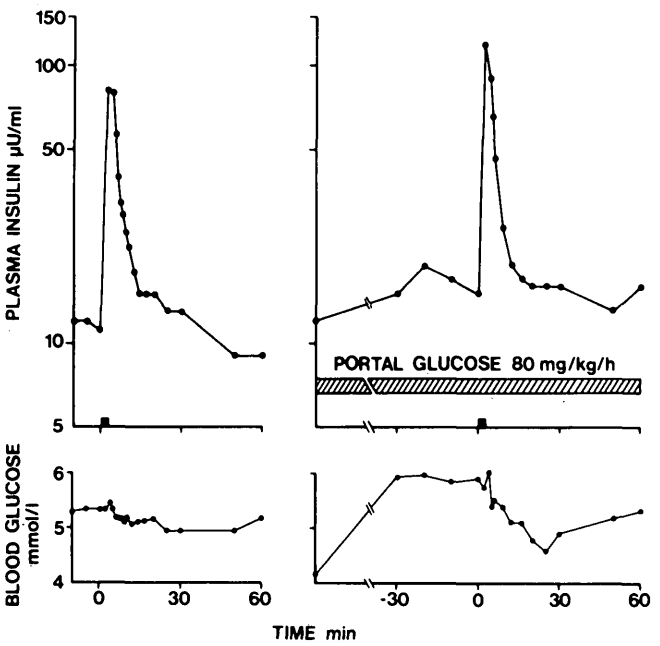


FIGURE 2. Time-course of arterial plasma insulin and blood glucose before and after intraportal infusion of 10 mU/kg at normoglycemia (left) and at steady hyperglycemia (right). Filled bar denotes the insulin infusion. Plasma insulin values are logarithmic.

calculation is independent of the complexity of the disappearance, PCR is the least controversial estimate of plasma disappearance rate. After portal infusion, the first pass hepatic uptake of insulin was treated as an instantaneous loss (see Figure 1), which means that PCR_{po} includes the corresponding clearance rate. For insulin reaching the systemic circulation, compartmental analysis (Figure 1) was used to estimate k_{el} (1/min), the average net fractional transfer rate constant from the apparent plasma volume, APV (ml/kg). In the two-compartment model, with irreversible loss from the extravascular compartment, k_{el} is equal to $k_{21} \cdot k_{32}/(k_{12} + k_{32})$. If it is assumed that irreversible exit is from the plasma pool (see Figure 1), k_{el} ($=k_{31}$) will be identically large. The relationship APV = PCR/k_{el} was then used to calculate APV.[9] The reason for calculating APV is as follows. After peripheral infusion of insulin, APV_{pe} should equal the value of plasma volume, but, after portal infusion, APV_{po} should not because the clearance rate corresponding to the first pass fractional hepatic uptake is included in PCR_{po}. It is evident that the larger the first pass fractional hepatic uptake of insulin the larger the APV_{po} value.

The percentage of insulin lost by adsorption to syringes and catheters was 14–16%.[9] The appropriate values were used in all calculations, but the uncorrected doses are given in the text.

The effect of insulin on arterial glucose or FFA was calculated as the decrement from the pretest level to the mean of the two lowest consecutive concentrations and was expressed as the percent change from the pretest level.[13] The k_G value of the IVGTT was calculated as proposed by O'Sullivan et al.[14]

Statistical methods. Standard statistical formulas were used.[15] Fasting plasma insulin was log transformed before statistical analysis because of skewness to the right. No other distribution was significantly skewed, but log transformation was performed before statistical analysis when it gave distributions and residuals closer to the normal and stabilized the variances. Unless otherwise stated, values given are means ± SD.

RESULTS

Representative sets of data for portal and peripheral infusions of insulin are given in Figures 2 and 3. For most of the subjects studied, detailed data on the modeling of the kinetics of insulin have been reported previously.[9] The values of PCR and APV in the present group of patients are summarized in, respectively, Table 2 and Figure 4. At steady hyperglycemia the two doses of glucose infusion gave similar results, which were therefore pooled. Insulin kinetics, insulin sensitivity, or glucose tolerance did not differ between patients with and without a portal catheter. It may be added that insulin kinetics and glucose tolerance were the same before and 3 days after inguinal herniorrhaphy, whereas the glucose decrement in response to insulin was 4.6 ± 3.8% less postoperatively ($P < 0.05$).

Insulin kinetics. After portal insulin infusion, PCR_{po} decreased markedly with increasing dose of insulin at normoglycemia (Table 2; $r = -0.71$, $P < 0.001$). Also, hyperglycemia was associated with a decrease of PCR_{po} (Table 2; comparison of regression lines, $P < 0.05$). The PCR_{po} or APV_{po} values obtained in the afternoon did not differ from those obtained in the morning, despite the fact that endogenous plasma insulin was significantly ($P < 0.01$) lower when fasting was prolonged to the afternoon (Table 1). APV_{po} did not vary with the dose ($r = -0.10$, $P > 0.05$), but was 18% lower at hyperglycemia than at normoglycemia (Figure 4, $P < 0.01$).

After peripheral insulin infusion, PCR_{pe} (Table 2) was not demonstrably affected by variation of the insulin dose at normoglycemia ($r = -0.04$, $P > 0.05$), but there was a nega-

FIGURE 3. Plasma insulin and blood glucose concentrations before and after peripheral infusion of 20 mU/kg at normoglycemia (left) and steady hyperglycemia (right). See legend to Figure 2.

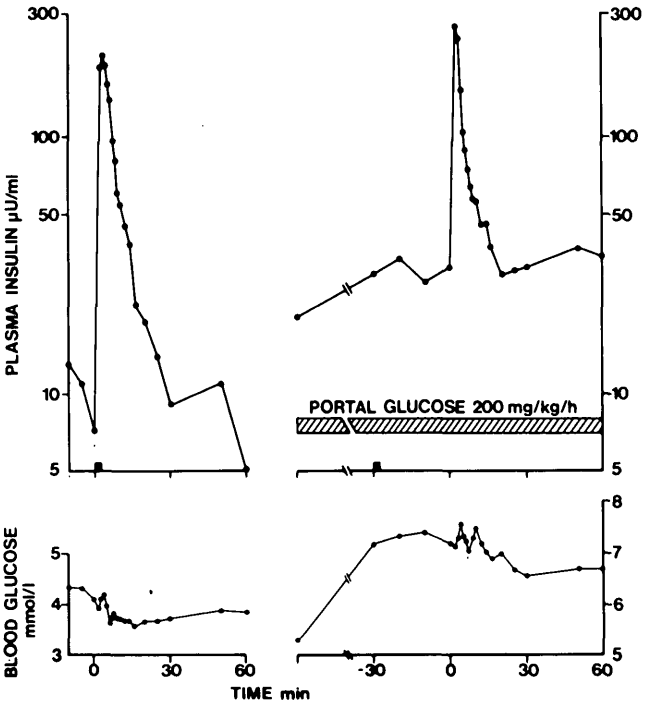


TABLE 2
Plasma clearance rate and effect of insulin as functions of insulin dose

Time of day	Glucose level	Dose (mU kg^{-1})	Portal infusion PCR (ml min^{-1} kg^{-1})	Portal infusion Blood glucose decrement (%)	Portal infusion Plasma FFA decrement (%)	Peripheral infusion PCR (ml min^{-1} kg^{-1})	Peripheral infusion Blood glucose decrement (%)	Peripheral infusion Plasma FFA decrement (%)
a.m.	N	5	32.1 ± 11.7 (5)	9.1 ± 1.0 (3)		15.4 ± 5.0 (11)	7.6 ± 2.6 (7)	12.3 ± 15.3 (5)
		10	30.0 ± 9.0 (11)	11.7 ± 2.4 (10)	9.4 ± 8.0 (7)	16.0 ± 4.6 (21)	11.6 ± 4.7 (16)	12.9 ± 13.5 (14)
		15				13.0 ± 2.9 (2)	15.1 ± 4.2 (2)	20.9 ± 30.0 (2)
		20	20.8 ± 4.2 (7)	18.4 ± 5.2 (6)	13.0 ± 12.3 (3)	14.7 ± 2.4 (10)	18.2 ± 6.3 (10)	18.0 ± 21.0 (3)
		30	18.7 ± 7.0 (5)	18.5 ± 3.3 (5)	19.1 ± 20.0 (3)	15.7 ± 3.8 (9)	22.0 ± 3.5 (6)	41.9 (1)
		40	17.0 ± 4.8 (3)	21.2 ± 2.8 (3)	47.3 (1)			
		50	14.1 ± 2.8 (5)	31.0 ± 7.4 (5)	38.8 (1)			
	SSH	5				16.6 ± 3.6 (5)	4.1 ± 3.0 (5)	
		10	21.0 ± 7.9 (5)	9.8 ± 8.5 (5)				
		15				15.2 ± 2.8 (5)	10.5 ± 2.8 (4)	
		20	21.7 ± 5.8 (7)	12.6 ± 5.0 (7)		15.4 ± 1.2 (2)	17.3 ± 9.3 (2)	
		30				11.4 ± 2.1 (3)	26.1 ± 4.9 (3)	
		40	13.8 ± 2.3 (4)	27.2 ± 2.1 (3)				
p.m.	N	10	33.0 ± 11.4 (3)	8.8 ± 3.2 (3)	23.2 ± 20.5 (3)			
		20	26.7 ± 9.4 (2)	15.0 ± 2.4 (2)	66.3 (1)			
		30	19.2 ± 4.4 (5)	15.7 ± 2.9 (5)	31.7 ± 17.1 (4)			

Values are means ± SD. Number of determinations is given within parentheses. PCR, plasma clearance rate; N, normoglycemia; SSH, steady state hyperglycemia.

tive correlation between dose and PCR_{pe} at hyperglycemia ($r = -0.56$, $P < 0.05$). APV_{pe} varied with insulin dose ($r = 0.56$, $P < 0.001$), whereas it did not change during glucose infusion (Figure 4).

Relations between insulin kinetics and other metabolic variables. PCR was tested for possible correlations with k_G (see Table 1), pretest blood glucose concentration, pretest endogenous plasma insulin concentration, relative weight, and age. Owing to the findings at hyperglycemia, also APV was tested for possible relations with pretest glucose and insulin concentrations. To account for the variation with insulin dose, the latter was included in the partial correlation coefficients given below. After portal insulin infusion, PCR_{po} varied negatively with relative weight (pooling of results at normoglycemia and hyperglycemia: pooled partial $r = -0.42$, $P < 0.01$). The corresponding regression equations (with log transformation of dose and PCR_{po}) predict that an increase of 10% in relative weight gives, on the average, a decrease of about 9% in PCR_{po}. The APV_{po} value obtained at normoglycemia showed a weak negative correlation with fasting blood glucose concentration (partial $r = -0.36$, $P < 0.05$). None of the remaining variables varied significantly with PCR or APV. After peripheral insulin infusion, the pooled partial r between PCR_{pe} and relative weight was -0.19 ($P > 0.05$).

Stepwise multiple regression analysis was performed in order to ascertain to what extent joint relations between the above independent variables influenced the correlations with PCR or APV. It was found that relative weight and fasting blood glucose had stable negative relationships with PCR_{po} and APV_{po}, respectively. For example, the significant negative correlation between PCR_{po} and relative weight was thus not due to joint correlations between relative weight and other variables, such as blood glucose or plasma insulin. In the material as a whole, the correlation coefficient between relative weight and fasting plasma insulin was 0.249, which almost reached the 5% level of significance. There was a weak negative correlation between age and PCR_{po} at normoglycemia when the influence of relative weight was eliminated (partial $r = -0.36$, $P < 0.05$).

Relations between PCR and insulin sensitivity. The effect of insulin on arterial blood glucose and plasma FFA concentrations is given in Table 2. The relationships between blood glucose decrement and insulin dose, or PCR, are given in Table 3. Blood glucose decrement, used as an index of insulin sensitivity, showed a good proportionality to insulin dose. But no significant relationship was found between the blood glucose decrement and PCR (Table 3). (The dose was again included in the partial correlations to eliminate the effect of different doses on PCR and blood glucose decrement.) Furthermore, the blood glucose decrement as well as the fasting plasma insulin concentration were smaller in the afternoon than in the morning ($P < 0.05$ and $P < 0.01$, respectively), whereas PCR or other kinetic parameter values did not change. The smaller PCR values at hyperglycemia were not accompanied by any change in the effect of insulin on blood glucose ($P > 0.05$).

FIGURE 4. Apparent plasma volume (APV) after portal and peripheral infusion of insulin. Values comprise the morning studies and are means ± SD.

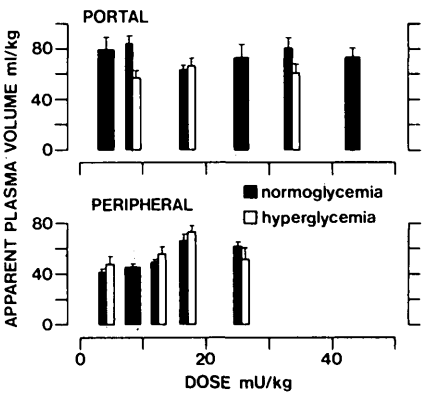


TABLE 3
Relationships between the blood glucose decrement, an index of insulin sensitivity, and insulin dose or PCR

Route of insulin infusion	Time of day	Glucose infusion	N	Variable	Variable: Dose (μU/kg)	Variable: PCR§ (ml min^{-1} kg^{-1})
Portal	a.m.	−	32	Blood glucose decrement, %	0.85*	−0.04
	a.m.	+	15		0.73†	−0.37
	p.m.	−	10		0.75‡	0.38
Peripheral	a.m.	−	41		0.72*	−0.07
	a.m.	+	14		0.91*	0.01

PCR, plasma clearance rate.
* $P < 0.001$, † $P < 0.01$, ‡ $P < 0.05$.
§ Partial correlation (the dose was held constant).

The values of FFA decrement (Table 2) showed somewhat weaker correlations with dose than did those of the blood glucose decrement, but their partial correlation coefficients with PCR were of similar magnitude and were never different from zero (data not shown).

DISCUSSION

This study showed that the non-steady state clearance rate of insulin entering the portal vein decreases not only after large insulin doses but also at elevated blood glucose concentrations. It also showed that PCR_{po} varies negatively with relative weight and age. No such relations were found after peripheral infusion, though a combination of increased insulin dose and of glucose infusion was associated with a decrease in PCR_{pe}, too. The liver thus seems to play a major role for the distribution and removal of insulin, at least shortly after changes in portal glucose or insulin. Otherwise, there was a notable lack of correlations between PCR and other factors, such as fasting plasma insulin, insulin sensitivity, or glucose tolerance.

For obvious reasons, the portal studies were limited to patients with malignant disease. But neither the disease nor the preceding catheterization of the portal vein had a demonstrable effect on the variables studied. Inguinal herniorrhaphy, being a substantially longer and more traumatizing procedure, was followed by a slight decrease in insulin sensitivity alone. The k_G values were comparable to those found by Palmer and Ensinck[16] in normal subjects of similar age. It should be observed that k_G is the same whether the IVGTT is performed with or without a preceding insulin infusion at the rates used here (unpublished observation).

The utilization of portal and peripheral infusions of insulin made it possible to estimate the importance of the liver for the turnover rate of insulin. PCR_{po} is a combined measure of first pass hepatic uptake and the subsequent removal of insulin in the periphery and insulin recirculating to the liver (see Figure 1). The differences between the results of portal and peripheral infusions were, thus, essentially due to the amount of insulin removed during the first liver passage after portal infusion. Since PCR_{po}, but not PCR_{pe}, decreased with increasing dose of insulin, it is obvious that this effect was due mainly to a decrease in the first pass fractional hepatic uptake. APV_{po} did not vary with insulin dose. In contrast, APV_{pe} increased with increasing dose, and this was apparently an effect of the reentry of insulin from the extravascular compartment(s).[9] Thus, the constancy of APV_{po} at different doses of insulin can, again, only be explained by a diminished first pass fractional hepatic uptake after large insulin doses into the portal vein. During steady hyperglycemia, the decrease in PCR_{po} was accompanied by a corresponding decrease in APV_{po}. Since APV_{pe} did not change when the blood glucose concentration was raised, this shows that the first pass fractional hepatic uptake of insulin was diminished at hyperglycemia. As for PCR_{pe}, the effects of insulin and glucose were demonstrable only after infusion of both. However, since only one fifth to one fourth of the cardiac output is diverted to the liver, the effect of a reduced hepatic uptake on PCR_{pe} will be comparatively small and will be masked by uptake in other tissues. A diminished hepatic uptake of insulin during infusion of glucose has previously been demonstrated.[7]

The above findings infer that, when the insulin secretion rate is raised by glucose, the increases in both insulin and glucose will divert a larger fraction of the endogenous insulin from the liver to the peripheral tissues. For insulin concentrations clearly within the physiologic range, as after the two smallest doses (5–10 mU/kg), the effect of insulin itself on PCR_{po} is, at most, slight and not proved.[9] But the marked effect of increased glucose infers that changes in blood glucose cause changes in peripheral insulin concentration that do not reflect changes in pancreatic secretion rate alone. It is presently unknown whether this effect of glucose extends to the diabetic state.

The present study does not reveal whether the diminished hepatic uptake of insulin at hyperglycemia is a direct effect of glucose or a result of changes secondary to the hyperglycemia. But the evidence is against the possibility that pretest occupancy, or, downregulation of liver receptors by insulin was responsible. The pretest endogenous plasma insulin (absolute or incremental) showed no relationship to PCR or APV. PCR did not vary between morning and afternoon, whereas fasting plasma insulin did. Studies in vivo[17,18] and in vitro,[19,20] with insulin concentrations as low as those obtained by the glucose infusions, have shown no effect on hepatic uptake within 1–3 h (in our study, portal insulin concentrations averaged 51 μU/ml before the infusion of insulin). Downregulation of receptors by insulin itself appears to require more time,[21,22] and its physiologic significance has been questioned.[22]

We have not found any previous report of a relation between the degree of obesity and the plasma insulin

disappearance rate in vivo. The findings suggest that the obese patients had a decreased uptake both in peripheral tissues and liver and agree with studies in vitro.[1] The variation of relative body weight accounted for 17–18% of the variation of PCR_{po}. The negative correlation could not (statistically) be explained by the plasma insulin concentrations, which may have been due to the fact that none of our patients was markedly obese.

Binding of insulin in vitro is frequently found to be correlated negatively with the fasting insulin concentration and positively with the effect of insulin. There are, however, several situations in which these variables change in opposite directions and/or where these relations are absent.[1,23–26] Non-steady state PCR was not related to fasting plasma insulin, insulin sensitivity, or glucose tolerance. This implies that factors other than the number of insulin receptors are also important for the size of PCR and that variation in PCR plays a minor role for the acute effect of insulin on glucose and FFA metabolism. A similar lack of relations was reported by DeFronzo et al.,[26] who studied steady state PCR_{pe} in fasting obese subjects, though they found PCR_{pe} to vary positively with insulin action and negatively with insulin binding when starvation lasted for 14 days. Stimmler et al.[6] found a correlation between the disappearance and effect of insulin in normal subjects and in untreated diabetic patients, whereas Pearson and Martin[5] did not. Diabetics have either a normal[3–5] or a decreased[2,6] removal rate of insulin, and the results do not seem to vary with the fasting plasma insulin concentration.

It has recently been postulated that the regulation of blood glucose is of secondary importance to the maintenance of optimal (peripheral) plasma insulin concentrations.[27] Our results support this hypothesis. Thus, while glucose is a powerful regulator of plasma insulin, by affecting both the release and the (hepatic) removal of insulin, the relationship between the removal rate and the effect of insulin is less obvious. The preference to divert a larger fraction of secreted insulin to the periphery during hyperglycemia, and a smaller one during normoglycemia, is compatible with the anabolic and catabolic demands of the fed and fasted state.[28] It is also compatible with the occurrence of spontaneous hypoglycemia in early diabetes.[29]

ACKNOWLEDGMENTS

This study was supported by grants from the Swedish Diabetic Association, the Funds of the University of Lund, the Royal Physiographic Society of Lund, and the Swedish Medical Research Council, project 03X-4726.

REFERENCES

[1] Olefsky, J. M.: The insulin receptor: its role in insulin resistance of obesity and diabetes. Diabetes *25*:1154–62, 1976.

[2] Frost, D. P., Srivastava, M. C., Jones, R. H., Nabarro, J. D. N., and Sönksen, P. H.: The kinetics of insulin metabolism in diabetes mellitus. Postgrad. Med. J. *49*:949–54, 1973.

[3] Genuth, S. M.: Metabolic clearance of insulin in man. Diabetes *21*: 1003–12, 1972.

[4] Ørskov, H., and Christensen, N. J.: Plasma disappearance rate of injected human insulin in juvenile diabetic, maturity-onset diabetic and non-diabetic subjects. Diabetes *18*:653–59, 1969.

[5] Pearson, M. J., and Martin, F. I. R.: The separation of total plasma insulin from binding proteins using gel filtration: its application to the measurement of rate of insulin disappearance. Diabetologia *6*:581–85, 1970.

[6] Stimmler, L., Mashiter, K., Snodgrass, G. J. A. I., Boucher, B., and Abrams, M.: Insulin disappearance after intravenous injection and its effect on blood glucose in diabetic and non-diabetic children and adults. Clin. Sci. *42*:337–44, 1972.

[7] Kaplan, N., and Madison, L. L.: Effects of endogenous insulin secretion on the magnitude of hepatic binding of labeled-insulin during a single transhepatic circulation in human subjects. Clin. Res. *7*:248, 1959. Abstract.

[8] Göthlin, J., Dencker, H., and Tranberg, K.-G.: Technique and complications of transumbilical catheterization of the portal vein and its tributaries. Am. J. Roentgenol. *125*:431–36, 1975.

[9] Tranberg, K.-G., and Dencker, H.: Modeling of plasma disappearance of unlabeled insulin in man. Am. J. Physiol. *235*:E577–85, 1978.

[10] Hjelm, M., and de Verdier, C.-H.: A methodological study of the enzymatic determination of glucose in blood. Scand. J. Clin. Lab. Invest. *15*:415–28, 1963.

[11] Heding, L. G.: A simplified insulin radioimmunoassay method. *In* Labelled Proteins in Tracer Studies. Donato, L., Milhaud, G., and Sirchs, J., Eds. Brussels, Euratom, 1966, pp. 345–51.

[12] Trout, D. L., Estes, H. E., Jr., and Friedberg, S. J.: Titration of free fatty acids of plasma: a study of current methods and a new modification. J. Lipid Res. *1*:199–202, 1960.

[13] Wilder, J.: Basimetric approach (law of initial value) to biological rhythms. Ann. NY Acad. Sci. *98*:1211–20, 1962.

[14] O'Sullivan, J. B., Snyder, P. J., Sporer, A. C., Dandrow, R. V., Jr., and Charles, D.: Intravenous glucose tolerance test and its modification by pregnancy. J. Clin. Endocrinol. Metab. *31*:33–37, 1970.

[15] Snedecor, G. W., and Cochran, W. G.: Statistical Methods, 6th edit. Ames, Iowa State University Press, 1967.

[16] Palmer, J. P., and Ensinck, J. W.: Acute-phase insulin secretion and glucose tolerance in young and aged normal men and diabetic patients. J. Clin. Endocrinol. Metab. *41*:498–503, 1975.

[17] Harding, P. E., Bloom, G., and Field, J. B.: Effect of infusion of insulin into portal vein on hepatic extraction of insulin in anesthetized dogs. Am. J. Physiol. *228*:1580–88, 1975.

[18] Samols, E., and Ryder, J. A.: Studies on tissue uptake of insulin in man using a differential immunoassay for endogenous and exogenous insulin. J. Clin. Invest. *40*:2092–2102, 1961.

[19] Mondon, C. E., Olefsky, J. M., Dolkas, C. B., and Reaven, G. M.: Removal of insulin by perfused rat liver: effect of concentration. Metab. Clin. Exp. *24*:153–60, 1975.

[20] Soll, A. H., Kahn, C. R., Neville, D. M., Jr., and Roth, J.: Insulin receptor deficiency in genetic and acquired obesity. J. Clin. Invest. *56*: 769–80, 1975.

[21] Gavin, J. R., III, Roth, J., Neville, D. M., Jr., De Meyts, P., and Buell, D. N.: Insulin-dependent regulation of insulin receptor concentrations: a direct demonstration in cell culture. Proc. Natl. Acad. Sci. USA *71*: 84–88, 1974.

[22] Huang, D., and Cuatrecasas, P.: Insulin-induced reduction of membrane receptor concentrations in isolated fat cells and lymphocytes: independence from receptor occupation and possible relation to proteolytic activity of insulin. J. Biol. Chem. *250*:8251–59, 1975.

[23] Freychet, P.: Cell membrane receptors and insulin action. *In* Diabetes. Bajaj, J. S., Ed. Amsterdam, Excerpta Medica Foundation, ICS 413, 1977, pp. 180–87.

[24] Beck-Nielsen, H., and Pedersen, O.: Insulin receptors on monocytes of young healthy persons correlated with glucose tolerance and insulin sensitivity. Diabetologia *14*:159–63, 1978.

[25] Beck-Nielsen, H., Pedersen, O., and Schwartz Sörensen, N.: Effects of diet on the cellular insulin binding and the insulin sensitivity in young healthy subjects. Diabetologia *15*:289–96, 1978.

[26] DeFronzo, R. A., Soman, V., Sherwin, R. S., Hendler, R., and Felig, P.: Insulin binding to monocytes and insulin action in human obesity, starvation, and refeeding. J. Clin. Invest. *62*:204–13, 1978.

[27] Turner, R. C., and Holman, R. R.: Insulin rather than glucose homeostasis in the pathophysiology of diabetes. Lancet *1*:1272–74, 1976.

[28] Cahill, G. F., Jr.: Physiology of insulin in man. Diabetes *20*: 785–99, 1971.

[29] Seltzer, H. S., Fajans, S. S., and Conn, J. W.: Spontaneous hypoglycemia as an early manifestation of diabetes mellitus. Diabetes *5*: 437–42, 1956.