Diabetologia (1983) 25: 489–495

Diabetologia

The 75-g Oral Glucose Tolerance Test: Effect on Splanchnic Metabolism of Substrates and Pancreatic Hormone Release in Healthy Man

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Summary. To determine the effect of the 75 g oral glucose tolerance test on carbohydrate and lipid metabolism, the splanchnic exchange of glucose, lactate, pyruvate, non-esterified fatty acids, β-hydroxybutyrate and acetoacetate as well as the release of insulin, C-peptide, glucagon and pancreatic polypeptide were evaluated in eight healthy male volunteers in the basal state and for 150 min following glucose ingestion. Oral glucose loading was followed by a rapid rise in splanchnic output of glucose (mean ± SEM; 154 ± 12 mmol/150 min), pyruvate (1.2 ± 1.2 mmol/150 min) and lactate (8.6 ± 2.0 mmol/150 min), whereas there were reductions in the splanchnic uptake of non-esterified fatty acids (−10.7 ± 4.4 mmol/150 min) and the splanchnic output of β-hydroxybutyrate (−4.8 ± 3.3 mmol/150 min) and acetoacetate (−3.0 ± 1.2 mmol/150 min). In parallel, splanchnic output of insulin (12.3 ± 2.7 nmol/150 min), C-peptide (36.1 ± 5.0 nmol/150 min) and transiently of pancreatic polypeptide rose, whereas that of glucagon fell (−0.58 ± 0.21 nmol/150 min). Even at 150 min after glucose ingestion, splanchnic ouptut and arterial concentrations of glucose, lactate, insulin and C-peptide were still above their respective basal values while those of non-esterified fatty acids and glucagon were reduced. Taking into account the partial suppression of endogenous glucose production by ingested glucose it is concluded that, in normal postabsortive man, only 49–63% of a 75 g oral glucose load is retained by the splanchnic bed during the first 150 min, the rest being available for non-hepatic tissues. Since typical metabolic responses to oral glucose loading were maintained up to 150 min after glucose ingestion, it appears that glucose absorption from the gut was not yet complete within this time. This finding partially jeopardizes the interpretation of calculated post-prandial hepatic glucose uptake for short observation periods.

Key words: Standard oral glucose tolerance test, splanchnic glucose output, splanchnic glucose retention, insulin production rate, non-esterified fatty acids, glucagon, pancreatic polypeptide.

Recent work using the hepatic venous catheter technique in normal man described the effects of different amounts of ingested glucose on insulin production rate [1] and splanchnic carbohydrate metabolism [2, 3]. No data are, however, available on the splanchnic exchange of substrates and hormones during the new 75 g oral glucose tolerance test, which has been recommended by the World Health Organization [4]. This study was consequently undertaken to investigate the effect of the proposed 75 g standard glucose load on splanchnic exchange of glucose and lipid metabolites as well as of released pancreatic hormones. This evaluation of splanchnic substrate metabolism and hormone release following standardized oral glucose loading is of considerable interest as the liver is thought to be the primary and most sensitive target organ of insulin action as compared to peripheral tissue [5, 6]. Furthermore, the hepatic bed has been assumed to exert a strong impact on glucose concentration in peripheral blood by controlling splanchnic glucose escape as only a small amount (around 15%) of a 100 g glucose load seems to be released by the splanchnic bed for utilization by peripheral tissues in healthy man within a 3 h period [3].

Subjects and Methods

Subjects

Subjects were 12 male volunteers between 19 and 32 years of age. All were within 10% of ideal body weight (101.0 ± 2.7%, mean ± SEM, as determined by Metropolitan Life Insurance Tables, 1959). None was diabetic or gave a history of liver disease as indicated by normal blood laboratory tests and oral glucose tolerance test (100 g). All subjects were asked to ingest a weight-maintaining diet containing 250–300 g of carbohydrate for at least 3 days before the study. The nature, purpose and possible risks of the study were carefully explained to all subjects before obtaining their consent to participate. The protocol of the study was approved by the Ethical Committee of the hospital.

Table 1. Net splanchnic output of metabolites and of pancreatic hormones in the basal state, during 150 min after ingestion of 75 g glucose and above basal in eight healthy men

	Splanchnic Output			
	Basal[a]	Following oral glucose ingestion		
		Total	p (versus basal)[b]	Above basal
Metabolites (mmol/150 min)				
Glucose	86.67 ± 7.94	241.11 ± 12.22	< 0.0005	154.61 ± 11.72
Pyruvate	1.22 ± 1.23	4.10 ± 1.06	< 0.0125	1.22 ± 1.22
Lactate	−10.35 ± 3.86	−1.58 ± 3.50	< 0.0025	8.58 ± 2.01
NEFA	−15.92 ± 4.85	−5.25 ± 0.76	< 0.05	10.68 ± 4.40
β-OHB	7.44 ± 2.42	2.45 ± 0.83	NS	−4.81 ± 3.25
Acetoacetate	3.71 ± 0.75	0.67 ± 0.84	< 0.025	−3.03 ± 1.18
Pancreatic hormones (nmol/150 min)				
Insulin	3.98 ± 0.83	16.32 ± 3.14	< 0.0025	12.31 ± 2.68
C-peptide	14.90 ± 2.55	51.31 ± 5.96	< 0.0005	36.08 ± 4.97
(Units insulin/time)	(2.04 ± 0.35)	(7.03 ± 0.82)	< 0.0005	(5.04 ± 0.68)
Glucagon	0.90 ± 0.24	0.29 ± 0.42	< 0.025	−0.58 ± 0.21
Pancreatic Polypeptide	0.95 ± 0.17	1.21 ± 0.33	NS	0.22 ± 0.28

Results are mean ± SEM

[a] Basal values are calculated from the mean of five observations in each subject during 30 min preceding glucose ingestion and expressed per 150 min

[b] Denotes the significance of differences between total splanchnic output and the respective basal values times 150 min

Procedures

Studies were performed with subjects in the recumbent position after an overnight fast (14–16 h). Catheters were inserted percutaneously into a peripheral vein, a femoral artery and through a femoral vein into a right-sided hepatic vein under fluoroscopic control as described previously [1, 2]. After the catheters were in place, arterial and hepatic venous blood was drawn at 7.5 min intervals both for a 30 min basal control period and for 150 min after ingestion of either 75 g glucose ($n=8$; glucose monohydrate 82.5 g/195 ml corresponding to 75 g glucose; Boehringer-Mannheim, Mannheim, FRG) or 200 ml of water ($n=4$). The total volume of blood obtained from each subject was 470 ml.

Methods for determination of estimated hepatic blood and plasma flow by means of the hepatic venous catheter technique using a primed constant infusion of indocyanine green dye [7, 8] have been described previously [1]. To avoid turbidity 5% sodium deoxycholate (Fluka, Buchs, Switzerland) was passed through a millipore filter (0.45 μ) and added to plasma before the measurement of indocyanine green dye [9]. Measurements of glucose were performed in whole blood by the hexokinase reaction, whereas lactate, pyruvate, non-esterified fatty acids (NEFA), β-hydroxybutyrate(β-OHB) and acetoacetate were analyzed enzymatically in plasma [10]. Insulin, C-peptide, glucagon and human pancreatic polypeptide were determined as previously reported [1, 11, 12].

Values for substrates, insulin (1 mU/l = 7.3 pmol/l), C-peptide (1 ng/ml = 331 pmol/l), glucagon (1 pg/ml = 0.287 pmol/l) and human pancreatic polypeptide (1 pg/ml = 0.238 pmol/l) were expressed in molarities. The following molecular weights were used for the calculations of molarities of pancreatic hormones: insulin 5734 [13], C-peptide 3021 [14], glucagon 3485 [15] and pancreatic polypeptide 4200 daltons [16].

Splanchnic exchange of substrates and hormones was calculated from the transsplanchnic (hepatic venous − arterial) concentration difference multiplied by the estimated hepatic blood or plasma flow, as appropriate; a positive splanchnic balance indicates a net output, a negative one net splanchnic uptake. Total output from the splanchnic bed for all variables during the 150 min following glucose ingestion was calculated by the trapezoidal rule as the area under the curve. Insulin production rate was derived from splanchnic C-peptide output [1]. Hepatic fractional extraction (%) of immunoreactive insulin (IRI), indicating the relative share of insulin retained by the liver [17], was estimates as $\left(\frac{\text{P-HV}}{\text{P}}\right)$ where HV represents hepatic venous and P prehepatic, i.e. portal and hepatic arterial concentration of insulin to which the liver cells are exposed. P was estimated as the sum of arterial insulin concentrations plus the differences in hepatic venous and arterial concentrations of C-peptide, both expressed in molarities. This calculation appears feasible as hepatic extraction of C-peptide is negligible [18]. Hepatic IRI uptake (pmol/min) was calculated as $(\text{P-HV}_{\text{IRI}}) \times$ estimated hepatic plasma flow. The hepatic clearance rate of IRI was calculated as the hepatic uptake divided by the estimated prehepatic insulin concentration [P] and expressed as milliliters per minute. Splanchnic fractional extraction of NEFA was calculated as the percentage of arterio-hepatic venous differences from arterial concentration.

All data in the text, tables and figures are presented as mean ± SEM. The paired Student's t-test was employed for statistical analysis [20].

Results

Splanchnic Output of Substrates

The effect of a 75 g oral glucose load on the splanchnic output of glucose over 150 min, as well as on that of some gluconeogenic substrates and their oxidation products, is presented in Table 1 per 150 min. Before glucose ingestion glucose, pyruvate, β-OHB and acetoacetate were mostly released from the splanchnic bed, whereas lactate and NEFA were taken up. Following oral glucose loading splanchnic output rose significantly above basal for glucose, pyruvate and lactate, thereby transiently reversing splanchnic lactate uptake (Fig. 1) into a net output. Splanchnic uptake of NEFA was reduced after glucose ingestion by 10.68 ±

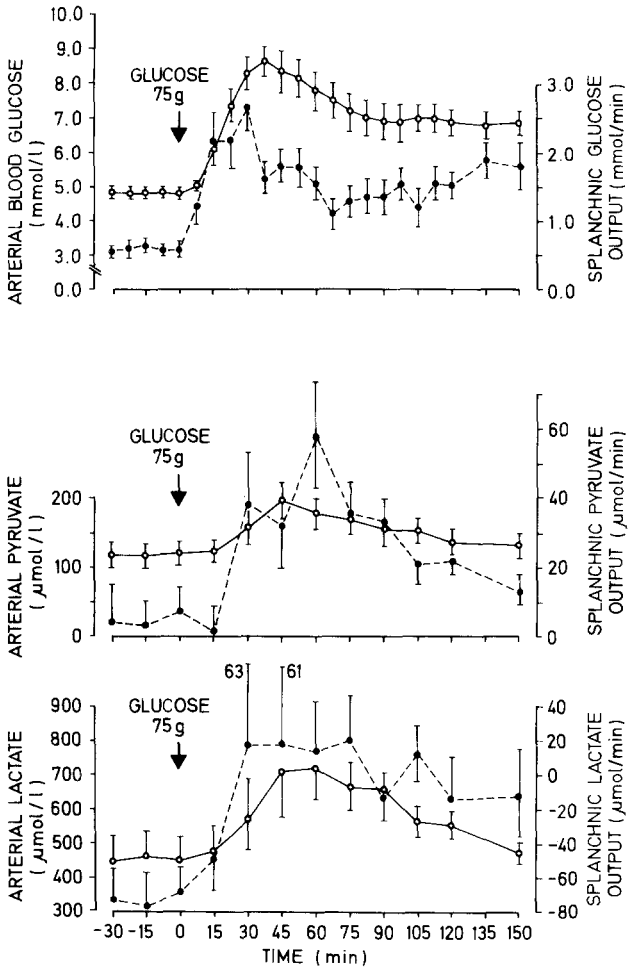

Fig. 1. Arterial concentrations (○—○) and splanchnic output (●- - -●) of blood glucose, pyruvate and lactate in the basal state and after ingestion of 75 g glucose in eight healthy men. Values are mean ± SEM

4.40 mmol/150 min as was splanchnic output of acetoacetate. This was accompanied by a fall in splanchnic fractional extraction of NEFA from a basal value of 17 ± 3% to a nadir of −14 ± 7% at 96 ± 6 min ($p <$ 0.0025). No significant change was seen in the splanchnic exchange of β-OHB during 150 min following glucose loading. Total splanchnic glucose output was 43.4 ± 2.2 g/150 min after glucose ingestion, which translates into a minimal post-prandial splanchnic retention of 31.8 ± 2.2 g/150 min, whereas splanchnic glucose output above basal was 27.8 ± 2.1 g/150 min.

Before glucose ingestion values of arterial glucose, pyruvate and lactate fluctuated only to a small extent, but rose to mean individual peak levels of 9.0 ± 0.3 mmol/l for glucose at 53 ± 15 min, of 204 ± 24 μmol/l for pyruvate at 64 ± 8 min, and of 789 ± 102 μmol/l for lactate at 69 ± 9 min (Fig. 1). These rises in arterial concentration were paralleled by an increase in splanchnic output of the respective variables, which reached their maximal values of 2.8 ± 0.3 mmol/min (glucose) at 55 ± 18 min, of 66 ± 14 μmol/min (pyruvate) at 64 ± 9 min and of 81 ± 24 μmol/min (lactate) at 64 ± 11 min.

It is of note that, 150 min after glucose ingestion, values were still in part significantly above their respective basal values for arterial blood glucose (Δ + 2.1 ± 0.3 mmol/l, $p < 0.0005$), pyruvate (Δ + 13 ± 13 μmol/l, NS) and lactate (Δ + 26 ± 60 μmol/l, NS) as well as for the splanchnic output of glucose (Δ + 1.13 ± 0.32 mmol/min, $p < 0.01$), pyruvate (Δ + 8 ± 9 μmol/min, NS) and lactate (Δ + 58 ± 24 μmol/min, $p < 0.025$). Mean arterial concentrations of NEFA fell from basal values of 720 ± 106 to 198 ± 24 μmol/l ($p <$ 0.0025) at 150 min after glucose ingestion, whereas those of acetoacetate (basal, 370 ± 21 μmol/l) and β-OHB (basal, 294 ± 62 μmol/l) stayed within their respective basal ranges.

Splanchnic Output of Pancreatic Hormones (Table 1)

Splanchnic output of insulin (basal, 3.98 ± 0.83 nmol/150 min) and C-peptide (basal, 14.90 ± 2.55 nmol/150 min) rose about fourfold above basal following glucose loading, whereas splanchnic output of glucagon (basal, 0.90 ± 0.24 nmol/150 min) was reduced by 68%. No change occurred in total splanchnic output of pancreatic polypeptide. The observed increase above basal in splanchnic C-peptide output reflects an insulin production rate of 5.04 ± 0.68 U/150 min, which corresponds to a total glucose output of 43.4 ± 2.2 g/150 min.

Hormone concentrations in hepatic venous blood were consistently greater than in arterial blood (Table 2). Following ingestion of 75 g glucose mean arterial insulin and C-peptide concentrations of individual peak levels rose to 427 ± 70 pmol/l at 52 ± 15 min, and to 2248 ± 185 pmol/l at 79 ± 11 min, respectively. The observed arterial C-peptide concentrations were related to splanchnic C-peptide output ($p < 0.001$) and thereby to insulin production rate. Serum concentrations of pancreatic polypeptide rose only transiently at 15 to 45 min ($p < 0.0125$ to < 0.0025) and reached individual peak levels of 70 ± 12 pmol/l at 21 ± 3 min after glucose ingestion. In contrast, plasma concentrations of glucagon fell by 53% to 10 ± 1 pmol/l, reaching their nadir at 87 ± 16 min. Elevated levels of insulin and C-peptide, as well as reduced values of plasma glucagon, were still observed at 150 min after glucose ingestion.

Estimated Hepatic Blood Flow and Handling of Insulin Across the Hepatic Bed

Estimated hepatic blood flow in the basal state was 1222 ± 145 ml/min and rose to individual peak values of 1995 ± 249 ml/min at 38 ± 11 min after glucose ingestion. This change was paralleled by a rise in estimated hepatic plasma flow from a basal value of 696 ± 73 ml/min to a peak of 1187 ± 137 ml/min within 7.5 to 112.5 min (Table 2).

Stimulation of insulin production rate by glucose ingestion (Table 3) was accompanied by a four- to fivefold rise in calculated hepatic insulin uptake up to 150 min

Table 2. Effect of a 75 g oral glucose load on arterial and hepatic venous concentrations of insulin, C-peptide, glucagon and pancreatic polypeptide and estimated hepatic plasma flow in eight healthy men

		Time (min)									
	Basal[a]	15	30	45	60	75	90	105	120	135	150
Insulin (pmol/l)											
Arterial	58± 7	226± 66	394± 80	292± 44	285± 66	248± 58	226± 44	234± 37	234± 44	248± 51	241± 37[f]
Hepatic venous	95±15	350± 88	548± 95	475± 80	102±102	423±110	350± 66	380± 66	343± 73	358± 73	387± 73[e]
C-peptide (pmol/l)											
Arterial	635±79	1079±192	1737±245	1790±136	1821±139	1834±199	1797±139	1840±113	1933± 99	1917±152	1833±119[f]
Hepatic venous	788±93	1403±245	2155±248	2367±182	2410±242	2333±298	2284±136	2314±132	2195±149	2251±152	2363±179[f]
Glucagon (pmol/l)											
Arterial	20± 2	19± 3	15± 1	12± 1	13± 2	11± 1	12± 1	12± 1	12± 1	–	13± 2[d]
Hepatic venous	34± 4	29± 3	23± 3	20± 2	18± 2	18± 2	17± 2	16± 2	17± 2	–	15± 2[f]
Pancreatic polypeptide (pmol/l)											
Arterial	27± 6	64± 12	49± 7	36± 4	28± 4	28± 4	28± 3	30± 6	28± 4	–	28± 4
Hepatic venous	31± 2	87± 15	56± 11	44± 9	31± 5	36± 6	38± 6	38± 2	36± 6	–	31± 5
Estimated hepatic plasma flow (ml/min)	696±73	962±149	1001±106	864± 56	757± 67	734± 68	700± 53	744± 50	810± 59	858± 76	852± 94

Results expressed as mean ± SEM

[a] Basal values represent the mean of five observations in each subject during 30 min preceding glucose loading. p was calculated at 150 min versus the respective basal values:

[b] <0.05, [c] <0.025, [d] <0.01, [e] <0.0025, and [f] <0.0005

after glucose ingestion, whereas hepatic fractional extraction of insulin (basal, 53±2%) did not change throughout the study except for a transient fall at 30 min. Mean hepatic insulin clearance rate, which compensates for changes in plasma flow, ranged from 325 to 421 ml/min and remained unchanged throughout the study.

Control studies in four healthy subjects ingesting 200 ml of water instead of glucose, demonstrated only insigificant changes in mean splanchnic output of glucose (−10%), pyruvate (0%), lactate (−12%), NEFA (−3%), β-OHB (+20%) and acetoacetate (−24%) during the 150 min of observation. As far as pancreatic hormones were concerned, a minor and insignificant fall in splanchnic output of insulin (−11%) and C-peptide (−19%) was seen.

Discussion

In this study, post-absorptive splanchnic glucose release was accompanied by a splanchnic output of pyruvate, β-OHB and acetoacetate, whereas lactate and non-esterified fatty acids were retained by the splanchnic bed. Following glucose loading both arterial blood glucose and splanchnic glucose output rose and stayed above basal levels throughout the 150 min of observation. Simultaneously, splanchnic output of pyruvate and lactate rose significantly above basal, whereas that of acetoacetate was reduced and that of β-OHB showed no significant change. The described rise in splanchnic NEFA output above basal reflects reduced hepatic uptake of this compound following glucose ingestion.

The observed splanchnic glucose output above basal of 27.8±2.1 g/150 min reflecting maximal retention of 63% or 47.2 g of ingested glucose by the splanchnic bed as well as the failure of arterial blood glucose to return to baseline levels within 150 min are in agreement with findings described previously after a 100 g glucose load [21]. As basal endogenous glucose production (normal, 104±10 mg/min) is reduced by 66±6% following a 45 to 96 g oral glucose load [22] splanchnic glucose retention determined as the difference between the 75 g of ingested glucose and total splanchnic glucose output (Table 1), corrected for residual glucose production (5.3 g/150 min), would only amount to 34.9 g/150 min. This 49% retention of ingested glucose could be due both to hepatic glucose uptake and incomplete absorption of glucose from the gut, which is known to last for at least 210 min [23]. Incomplete absorption instead of increased hepatic glucose retention as an additional cause of the 49–63% splanchnic retention of ingested glucose per 150 min would be in line with the observation that in normal man about 90% of an 100 g oral glucose load is absorbed and passes through the liver within 180 to 240 min [22]. Our findings are also in contrast to the contention that the liver was the preferred site of oral glucose deposition [24] and to the described earlier decline of arterial glucose and splanchnic glucose output to baseline values by 120 to 165 min after ingestion of 100 g glucose [25]. The latter observation may be due in part to the broad range of gastric emptying time (40 to 85 min; [26]) and to pulsatile gastric emptying. The minimal share of ingested glucose escaping the splanchnic bed above basal after ingestion of 75 g glucose and thus being available for non-insulin

Table 3. Effect of a 75 g oral glucose load on the fate of insulin across the splanchnic bed in eight healthy men

	Basal[a]	Time (min)									
		15	30	45	60	75	90	105	120	135	150
Insulin production rate (pmol/min)	100±17	340±97[c]	404±37[f]	488±73[f]	462±78[e]	378±102[d]	334±51[e]	352±62[d]	249± 84	298±51[d]	478±126[d]
Hepatic uptake (pmol/min)	79±14	163±35[c]	244±38[d]	340±43[f]	318±74[d]	251± 68[c]	249±45[d]	242±47[c]	238±138	179±46[c]	340± 83[d]
Hepatic fractional extraction (%)	53± 2	41± 6	38± 7[b]	47± 4	46± 6	45± 6	51± 7	45± 6	37± 10	38± 8	50± 6
Hepatic clearance rate (ml/min)	360±34	325±47	360±63	404±35	377±40	335± 55	353±55	335±48	294± 78	341±82	421± 67

Results expressed as mean ± SEM

[a] Basal values represent the mean of five observations in each subject during 30 min preceding glucose loading. p was calculated versus the respective basal values:

[b] <0.05, [c] <0.025, [d] <0.01, [e] <0.0025 and [f] <0.0005

dependent tissues such as the brain [27] was 37±3% in this study. This compares well with the 31 to 33% provided by the splanchnic bed per 150 to 180 min after a 100 g glucose load in man [21, 28] and with the 37% of ingested glucose entering the general circulation in the rat [29], but contrasts with the 15±3% escaping the splanchnic bed after ingestion of 100 g glucose as reported by others [3, 24]. The overall error in absorption of ingested glucose introduced by an observation period of only 150 min as compared to the at least 180–210 min required for complete absorption from the gut may, however, be as little as 12%. This estimate, which can be derived from data obtained during IV and oral glucose loading [23], increases the minimal share of glucose being available for non-hepatic peripheral tissues after a 75 g glucose load to 49%.

From these findings it is apparent that the term splanchnic glucose retention does not imply that all glucose retained by the splanchnic bed is taken up by the liver. The same splanchnic glucose output estimated by means of the hepatic venous catheter technique not only reflects intestinal glucose absorption, but also includes the effects of splanchnic uptake of absorbed and recirculated glucose as well as suppression of hepatic glucose production; the latter being partially turned off by increases in circulating serum insulin [6, 30, 31] and possibly also by a rise in portal venous concentrations of blood glucose [32].

In addition, we also examined the effect of a 75 g glucose load on the splanchnic exchange of lactate, pyruvate, NEFA, β-OHB and acetoacetate. Our data confirm the well known glucose-dependent rise in plasma lactate and pyruvate concentrations [33, 34], which is associated with a rise in splanchnic pyruvate output and a reduction in splanchnic lactate uptake. The increased rate of hepatic glycolysis under these conditions of hyperinsulinaemic hyperglycaemia is reflected by a combined rise in splanchnic lactate and pyruvate output above basal of 9.8 mmol/150 min, corresponding to 882 mg glucose or 1.18% of the ingested glucose load. These alterations in splanchnic release of lactate and pyruvate may be due to the glucose supply offered to the liver or to a change in gluconeogenesis. That peripheral tissues contribute to the rise in lactate concentration [35] has not been substantiated by direct measurements of forearm lactate exchange [36].

NEFA released from triglyceride stores are transported to the liver, which in the dog removes 25% of offered NEFA [37], corresponding well to the 17% splanchnic fractional extraction of NEFA seen in this study in healthy men. Following glucose ingestion splanchnic fractional extraction of NEFA fell in parallel with its plasma concentration and even reverted to occasional net splanchnic output at arterial NEFA concentrations below 200 μmol/l. Simultaneously, splanchnic NEFA uptake was reduced by approximately 67%, as were arterial NEFA levels, and total splanchnic ketone body output fell by 70% as less substrate was provided for oxidation [38] (Table 1). The latter effect was most probably due to inhibition of lipolysis by insulin [39], which also directly impairs hepatic ketogenesis [40]. The rise in the β-OHB/acetoacetate ratio, which reflects the intracellular redox state (a rising ratio indicating a more reduced state) after glucose ingestion, may be due to a marked decrease in the splanchnic acetoacetate output or to a preferential uptake of acetoacetate in peripheral tissues. The latter occurs primarily in human muscle [41] and might even be exaggerated by a glucose-induced rise in serum insulin levels.

Our estimate of post-absorptive insulin release was 14±2 mU/min and of the same order of magnitude as the 17±2 mU/min [1] or the 23.6±7.7 units/24 h, i.e. 16.3 mU/min [42], reported previously. Total splanchnic C-peptide output following ingestion of 75 g glucose indicates an insulin production rate of 7.03±0.82 units/150 min, which is less than the 13.0±2.0 units/150 min released after a 100 g glucose load [21].

Regarding the fate of insulin across the liver bed, it is of note that, in accordance with previous findings obtained in man with infusion of biosynthetic human insulin [19], hepatic insulin uptake changed in parallel with insulin production rate. This is in line with the pro-

portional rise in absolute hepatic insulin uptake with increasing portal insulin concentrations shown experimentally in rats [43] and dogs [44]. Following glucose ingestion (75 g) a transient reduction in hepatic fractional insulin extraction (basal, 53 ± 2%) was observed at 30 min, which was less pronounced than that seen in both healthy subjects and non-insulin-dependent diabetic patients after a 100 g glucose load [17]. This difference may be due to the smaller amount of glucose ingested in this study. Since hepatic fractional extraction and insulin clearance (basal, 360 ± 34 ml/min), which were both in the previously reported range [18, 19], remained mostly unchanged following the 75 g glucose load, any change in insulin production rate was matched by an appropriate deviation in arterial C-peptide and insulin concentration.

Furthermore, it is of note that both 120 min [1] and 150 min after glucose loading concentrations of immunoreactive insulin and C-peptide were still above their respective basal levels. This, as well as the supranormal values of arterial glucose and the associated reduction in arterial glucagon concentration [45], indicates continuing glucose absorption from the gut at the end of the 150 min observation period and thereby also hints at an underestimate of the insulin production rate required for the assimilation of the glucose load. In this context it is of interest that secondary hyperglycaemia at 150 min after glucose ingestion due to the stress of the experimental procedure was ruled out by the absence of any change in arterial concentrations or splanchnic exchange of substrates and hormones in healthy men ingesting water instead of glucose.

As the basal secretory rate of glucagon is estimated not to exceed 100–150 μg/day [46], the calculated 27 μg of basal post-hepatic glucagon release per 24 h implies 80% hepatic retention of this hormone. The role of glucagon in determining glucose disposal after glucose ingestion, however, seems remote as neither physiological elevations of plasma glucagon nor its suppression by glucose loading alters glucose tolerance in normal man capable of secreting sufficient amounts of insulin [47] or in diabetic man with appropriate insulin supply [48]. Glucose-induced hypoglucagonaemia may, however, contribute to the reduction in splanchnic ketone production since glucagon is known to promote both hepatic ketogenesis [49] and lipolysis [50]. Arterial concentrations of pancreatic polypeptide were 113 pg/ml (27 pmol/l) in the basal state and rose only transiently by 37 pg/ml 15 min after glucose ingestion as described by Floyd et al. [16]. The biological significance of this transient rise is unknown, as it does not affect blood glucose concentrations [16]. The overall post-hepatic production rate of pancreatic polypeptide in the basal state was 38 μg/24 h, of the same order of magnitude as that of glucagon.

In conclusion, glucose ingestion leads to an increase in splanchnic blood flow and also to a change in multiple endocrine and metabolic variables which interact in concert to control glucose assimilation. From this it appears that among the variables controlling post-prandial glucose metabolism determination of glucose obviously describes just one aspect of the system. Furthermore it is apparent that, 150 min after glucose ingestion, such key variables of carbohydrate metabolism as splanchnic glucose output and arterial as well as hepatic venous concentrations of glucose, insulin and C-peptide are still above their respective basal values and thus continue to be subject to both variability in glucose absorption and glucose metabolism. These data remind us that glucose absorption from the gut continues beyond 150 min after glucose ingestion in healthy man and that therefore estimates of hepatic (splanchnic) glucose uptake are subject to error unless the period of observation is extended until absorption of glucose is completed.

Acknowledgements. The authors are indebted for technical assistance to Mrs. A. Hofer, Mrs. E. Nowotny, Mrs. L. Geier, and Mrs. H. Haslinger, and to Dr. K. Kletter for statistical advice. This study was supported by grant No. P 5164 of the 'Fonds zur Förderung der wissenschaftlichen Forschung Österreichs'.

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Received: 9 November 1982
and in revised form: 13 May 1983

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