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Concentrations of Glucagon and the Insulin:Glucagon Ratio in the Portal and Peripheral Circulation[1] (38286)

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(Introduced by P. J. Mulrow)

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It is well-recognized that insulin and glucagon exert opposing actions on hepatic glucose metabolism, the latter hormone stimulating and the former inhibiting the release of glucose by the liver. Recent studies with the perfused liver suggest that net hepatic glucose balance may be determined by the relative availability of both hormones rather than the absolute concentration of either hormone alone (1, 2). In support of this hypothesis, Unger, employing peripheral venous blood samples, suggested that the insulin glucagon (I/G) molar ratio varies with glucose need, being lowest in starvation and highest after glucose ingestion (3–5). Inasmuch as glucagon does not affect peripheral glucose disposal (6) but influences carbohydrate homeostasis solely by virtue of its hepatic effects, I/G ratios based on peripheral venous measurements are meaningful only to the extent that they reflect changes in the portal circulation. Although portal insulin concentrations have been characterized in human subjects (7), information regarding the I/G ratio in portal blood is not available. The present study was consequently undertaken to compare portal–peripheral gradients for glucagon and insulin and to determine the relation between portal and peripheral I/G ratios in human subjects in the basal state.

Materials and Methods. The subjects were six patients (2 males, 4 females), 53–84 years of age, who were studied following elective abdominal surgery. The procedures and conditions necessitating abdominal exploration were as follows: in three patients cholecystectomy for chronic cholelithiasis; in one bilateral oophorectomy for metastatic carcinoma of the breast; and in two exploratory laparotomy which demonstrated gastric rugal hypertrophy in one patient and carcinoma of the pancreas in the other. None of the patients were obese and none had a history or evidence of diabetes as indicated by normal fasting blood sugar levels and a K value greater than 1.0 on intravenous glucose tolerance testing (8). All patients were informed of the nature, purpose, and possible hazards of the study and gave their voluntary, written consent prior to participation.

At operation, following completion of the intra-abdominal procedure, the obliterated umbilical vein was identified and a Bakes dilator was introduced and carefully passed along the length of the umbilical vein into the left branch of the portal vein. Following recanalization of the previously obliterated umbilical vein, a small-gauge polyethylene catheter was inserted and its tip was left in place at the umbilical–portal vein junction. The distal portion of the catheter exited via the abdominal surgical incision which was closed in the usual manner. During the postoperative, prestudy period, patency of the portal vein catheter was maintained with a slow infusion of 0.9% sodium chloride containing 10 mg heparin/liter.

All patients were studied 4–5 days after surgery. In each case the postoperative course was uncomplicated and the patient was afebrile at the time of the study. The prestudy nutrition consisted of either 5% dextrose by vein or a clear liquid diet; in either case, carbohydrate intake amounted to 150 g/24 hr. For about 9 hr prior to the study, the patients received nothing by mouth and only saline by vein. At the time of

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study, simultaneous blood samples were withdrawn from the portal vein catheter and from an indwelling needle in an antecubital vein. Some of the subjects subsequently received an infusion of glucose or alanine, the results of which will be reported separately.

Following completion of the study, the polyethylene umbilical–portal vein catheter was withdrawn several centimeters and clamped. It was removed 24 hr later. No infections, bleeding, or thrombotic complications attributable to umbilical vein catheterization were observed.

Plasma pancreatic glucagon was determined by radioimmunoassay using Unger antibody 30K (9). Insulin was measured in plasma by radioimmunoassay using talc to separate free from bound insulin (10). I/G molar ratios were calculated as described by Muller *et al.* (5).

Results and Discussion. In Table I the concentrations of glucagon and insulin in portal and peripheral blood and the calculated I/G molar ratios are shown. Although there was considerable variation in the absolute plasma concentrations of glucagon, in all subjects the portal level exceeded the peripheral concentration. Furthermore, the portal: peripheral ratio was fairly consistent, the mean value being 1.3 ± 0.1. In a like manner, insulin levels in the portal vein were higher than in peripheral blood. However, the portal:peripheral ratio for insulin exceeded that of glucagon in all instances, the mean value (2.5 ± 0.3) being almost double that observed for glucagon ($P < 0.02$, paired t test). As a consequence, the I/G molar ratio in portal blood (2.2 ± 0.6) was significantly greater than that observed in peripheral blood (1.0 ± 0.2) ($P < 0.05$, paired t test). Despite the higher portal I/G ratio, a significant direct linear correlation was observed between portal and peripheral I/G ratios ($r = 0.78$, $P < 0.05$).

The present data demonstrate that in the basal state, portal glucagon levels exceed those in peripheral blood. However, the portal–peripheral gradient for glucagon is substantially smaller than that observed for insulin. In accord with previous studies, the portal–peripheral insulin gradient varied from 2 to 4 (7), while the gradient for glucagon was less than 2 (11). These data thus suggest that as compared to insulin, relatively small amounts of glucagon are bound and/or metabolized on passage through the liver. Supporting this conclusion is the demonstration that binding of glucagon by only a small propor-

TABLE I. Portal and Peripheral Venous Concentrations of Glucagon and Insulin and the Insulin:Glucagon (I/G) Molar Ratio.

Subject	Glucagon (pg/ml)			Insulin (μU/ml)			I/G Ratio	
	Portal vein	Peripheral vein	Po/Pe[a]	Portal vein	Peripheral vein	Po/Pe[a]	Portal vein	Peripheral vein
Go	140	123	1.1	28	7	4.0	4.7	1.3
Pe	70	55	1.2	9	4	2.3	3.0	1.7
Ro	155	113	1.4	9	4	2.3	1.4	0.8
Ch	105	98	1.1	9	5	1.8	2.0	1.2
He	130	84	1.5	8	3	2.7	1.4	0.8
Jo	425	270	1.5	8	4	2.0	0.4	0.3
Mean ± SEM	171 ± 52	124 ± 31	1.3 ± 0.1	11.8 ± 3.2	4.5 ± 0.6	2.5 ± 0.3	2.2 ± 0.62	1.0 ± 0.2

[a] Po/Pe = ratio of portal to peripheral concentrations.

tion of receptor sites on the hepatocyte is sufficient to elicit a biologic effect (12).

Reflecting the relative gradients for insulin and glucagon, the I/G molar ratio was consistently higher in portal than in peripheral blood. On average, peripheral measurements underestimated the I/G ratio in portal blood by 50%. Despite these differences, a direct linear correlation was observed between portal and peripheral I/G molar ratios. Thus while peripheral measurements may not reflect the absolute balance of glucoregulatory hormones in the portal bed, they nevertheless provide an index of the relative availability of insulin and glucagon to the liver.

Summary. In postoperative patients studied in the postabsorptive state by mean of an umbilical vein catheter, concentrations of glucagon and insulin in portal blood exceeded those in peripheral venous blood. However, the portal–peripheral gradient for insulin (1.8–4.0) was consistently greater than that observed for glucagon (1.1–1.5). Consequently, the insulin:glucagon (I/G) molar ratio in the portal vein was 100% higher than in peripheral blood. A direct linear correlation however, was observed between portal and peripheral I/G molar ratios. The data indicate that peripheral measurements underestimate the absolute ratio of insulin to glucagon in portal blood, but nevertheless provide an index of relative hormonal availability in the hepatic circulation.

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