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Pancreatic Hormones and Amino Acid Levels following Liver Transplantation

ANTONIO FRANCAVILLA, LORENZO POLIMENO, DAVID H. VAN THIEL, SATURO TODO, IGAL KAM, STEPHEN LYNCH AND THOMAS E. STARZL

Department of Gastroenterology, University of Bari, Bari, Italy, and Departments of Gastroenterology and Surgery, University of Pittsburgh Health Center, Pittsburgh, Pennsylvania 15240

Glucose intolerance, hyperinsulinemia, peripheral insulin resistance and hyperglucagonemia are common in patients with advanced liver disease. These abnormalities in the plasma levels of the pancreatic hormones, insulin and glucagon have been thought to be responsible, at least in part, for the abnormal plasma ratio of branched-chain amino acids to aromatic amino acids. To evaluate this issue, plasma levels of glucose, insulin, glucagon, C-peptide and the branched-chain and aromatic amino acids were measured before and serially after orthotopic liver transplantation in 9 humans and 5 dogs. The abnormal plasma amino acid levels rapidly improved and achieved normal levels following orthotopic liver transplantation. Insuiin levels also became normal following orthotopic liver transplantation, despite enhanced insulin secretion documented by an even further increased level of C-peptide. In contrast, the baseline abnormal plasma glucagon levels which are commonly seen in cirrhotics became even more abnormal following orthotopic liver transplantation. Despite this progressive increase in the abnormally elevated plasma glucagon levels, plasma amino acid levels, both branched-chain and aromatic, became normal. These data demonstrate that before and after orthotopic liver transplantation, there is: (i) no relationship between the changes in plasma levels of glucagon and changes observed in the plasma level of amino acids; and (ii) plasma insulin and amino acid levels change in the same direction. In addition, these changes in plasma insulin and amino acid levels following orthotopic liver transplantation occur despite enhanced secretion of insulin evidenced by the progressive increase in plasma levels of C-peptide.

Glucose intolerance (1, 2), hyperinsulinemia (3, 4), insulin-resistance (5, 6) and hyperglucagonemia (7–9) are common in patients with advanced liver disease. These hormonal abnormalities are thought to either contribute to or be responsible for the reduced plasma concentrations of the three principal branched-chain amino acids (BCAAs) valine, leucine and isoleucine, that are characteristic of endstage liver disease. As a result, these same hormonal abnormalities are thought also to contribute to the decreased molar ratio that exists in plasma between the BCAAs and the aromatic amino acids (AAAs) tyrosine, phenylalanine and tryptophan in cirrhotics (10–13). Herein, we report our observations concerning the plasma levels of insulin and glucagon and the major amino acids before and after orthotopic liver transplantation. The changes observed occur in cirrhotics postoperatively, were compared to those observed to occur in a noncirrhotic human recipient with normal liver function, who underwent liver transplantation for multiple hepatic adenomatosis and were also compared to those observed in five normal dogs, which were submitted to liver replacement under controlled laboratory conditions.

MATERIALS AND METHODS

Case Material. The clinical and physical characteristics of the eight cirrhotic patients and the single individual with multiple hepatic adenomatosis studied are shown in Table 1. As can be seen from the table, the patient with multiple hepatic adenomatosis had normal liver function. In contrast, the cirrhotic patients all had liver dysfunction as documented by the abnormalities in their bilirubin, prothrombin time and albumin levels. All patients were ingesting a 50 to 60 gm per day protein diet during the study when eating (preoperatively and after the fourth postoperative day). This intake is more than sufficient to guarantee adequate nutrition for all but the largest of individuals, particularly considering the inactivity and deconditioning present universally in the patients studied.

Cyclosporine and prednisone were used as the immunosuppressive agents for all of the recipients studied (14, 15). The preoperative, intraoperative and postoperative requirements for blood utilized by the patients studied are shown in Table 2.

The five mongrel dogs transplanted and studied weighed between 15 to 20 kg and, like the humans studied, were given cyclosporine and prednisone to prevent rejection using doses that, on a milligram per kilogram basis, were similar to those used by the patients (16). The surgical procedures used for the patients and animals were identical (15, 16).

Special Analyses. The plasma levels of immunoreactive insulin (IRI) were determined by radioimmunoassay using an insulin kit obtained from Serono Diagnostics (Braintree, Mass.). The detection limit of the assay was 5 μU per ml. The

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Address reprint requests to: Antonio Francavilla, M.D., Veterans Administration Hospital, Building 6, Circle Drive, Pittsburgh, Pennsylvania 15240.

TABLE 1. Patients treated with OLTx

Name	Sex	Age (yr)	Diagnosis	Bilirubin (mg/100 ml)	Prothrombin time (sec)	Albumin (gm/dl)	Height (inches)	Weight (kg)
B. R.	M	18	CAH	38.8	18	2.7	69	55
R. Y.	F	25	CAH	9.9	15	2.6	64	63
T. H.	F	23	CAH	2.2	16	2.2	64	61
G. H.	M	37	SC	19.7	15	2.6	62	92
S. J.	F	41	SC	15.3	14	2.9	69	62
K. D.	M	34	SC	23.7	14	2.8	68	75
S. R.	F	29	Wilson's disease	3.5	17	2.7	66	69
S. P.	F	43	AD	4.9	14	2.8	65	61
G. B.	F	29	Hepatic adenoma	0.5	13	3.0		

Clinical characteristics, bilirubin, prothrombin time, albumin levels, height and weight of the eight cirrhotic patients and the single patient with multiple adenomatosis are indicated. CAH = chronic active hepatitis; SC = sclerosing cholangitis; AD = α_1-antitrypsin deficiency; OLTx = orthotopic liver transplantation.

TABLE 2. Units of blood used by the patients studied

Patient	Preoperative	Intraoperative	Postoperative
B. R.	26	22	8
R. Y.	18	8	3
T. H.	5	6	5
G. H.	9	14	16
S. J.	4	18	0
K. D.	4	11	3
S. R.	5	13	60
S. P.	19	7	2
G. B.	0	5	2

coefficient of variation for replicate samples assayed in our laboratory with this test is 8.37%. The plasma levels of C-peptide were determined by radioimmunoassay using a C-peptide kit obtained from Serono Diagnostics. The detection limit of the assay was 0.2 ng per ml. The coefficient of variation for replicate samples assayed in our laboratory with this test is 6.5%.

The plasma levels of immunoreactive glucagon (IRG) were determined with a glucagon kit also obtained from Serono Diagnostics. This kit was chosen specifically because of its high degree of accuracy, precision and specificity, as has been reported by Kenny and Say (17). Samples for the glucagon assay were collected in chilled tubes containing 500 units of a trypsin inhibitor (aprotinin) and 1.2 mg sodium EDTA per ml of whole blood collected for assay. The detection limit for the assay was 15 pg per ml. The coefficient of variation for this kit in our laboratory assaying replicate samples is 9.6%.

Representative samples of control sera were assayed for insulin, glucagon and C-peptide with and without cyclosporine added to the sample to achieve concentrations of cyclosporine found in blood clinically. No systemic difference was noted in the results. Moreover, all results were within the limits for variability for identical samples run in duplicate (Table 3).

For representative blood samples obtained from each patient studied, both before and after transplantation, a gel filtration technique (18) was used to determine the amount of IRG-detectable glucagon having molecular weights of 3,500, 7,000 and 40,000 daltons. Insulin/glucagon molar ratios were calculated as suggested by Muller et al. (19) using the formula:

$$[\text{IRI } (\mu\text{U per ml})/\text{IRG (pg per ml)}] \times 23.33 = \text{ratio}$$

This formula assumes that insulin has a molecular weight of 6,000 daltons and a biologic activity of 25 units per mg. It also assumes that glucagon has a molecular weight of 3,500 daltons.

TABLE 3. Replicate control samples (n = 20) assayed for their hormone content in the presence and absence of added cyclosporine at a concentration of 1,000 mg/ml whole blood

Hormone	Cyclosporine (−)	Cyclosporine (+)
Insulin (μU/ml)	17.0 ± 6.8	18.5 ± 5.9
Glucagon (pg/ml)	167 ± 61	158 ± 67
C-peptide (ng/ml)	1.36 ± 0.777	1.29 ± 0.84

Amino acid profiles were determined on deproteinized samples of plasma treated with 4% sulfosalicylic acid. The resultant supernatants were applied to an amino acid analyzer (Beckman Instruments, Somerset, NJ) and the levels of free BCAAs and AAAs, including tryptophan, were determined. As was done with the hormone assays, representative duplicate control blood samples were assayed for their amino acid content in the presence and absence of added cyclosporine to achieve levels seen in patients following transplantation. No consistent difference was noted between such duplicate samples, and all such samples assayed provided results within the range expected for replicate identical samples (data not shown). The glucose determinations were made using a glucose-oxidase method (20).

Statistical Analysis. The unpaired Student's t test was used for statistical analysis of the data. A p value < 0.05 was considered to be significant.

RESULTS

Endstage Liver Disease

Insulin and C-Peptide Levels: Because blood transfusions can alter hormone and amino acid levels, the blood requirements for the patients studied are shown in Table 2. In the eight patients studied, the C-peptide plasma concentrations were all high-normal preoperatively and rose 2½-fold during the first 12-hr following liver transplantation to a maximum level of 10 ng per ml and remaining elevated for at least 30 days (Figure 1A).

The plasma IRI levels followed a somewhat different pattern (Figure 1B). Following transplantation, there was a 2-fold increase in the IRI levels, but this increase lasted for only a few hours and subsequently returned to near-normal levels at 4 days posttransplantation. Because of these quite different patterns, there was a rapid increase in the C-peptide/IRI (Figure 1C), which reached

a maximum at 4 days and remained elevated throughout the 30-day study period. When reexamined at 6 months, both the insulin and C-peptide plasma levels were still slightly elevated (Table 4).

Glucagon: Before operation, the plasma levels of IRG were 4 times the normal values (Table 4). After transplantation, the IRG level rose progressively. The highest mean plasma levels of IRG were found at 30 days following transplantation (Figure 2), but when restudied at 6 months had returned to the normal range (Table 4). The resultant IRI/IRG molar ratio was decreased further than that determined preoperatively, as a consequence of the observed hyperglucagonemia. However, 6 months after transplantation, the IRI/IRG reached the highest levels as a result of persistent hyperinsulinemia and normalization of glucagon levels.

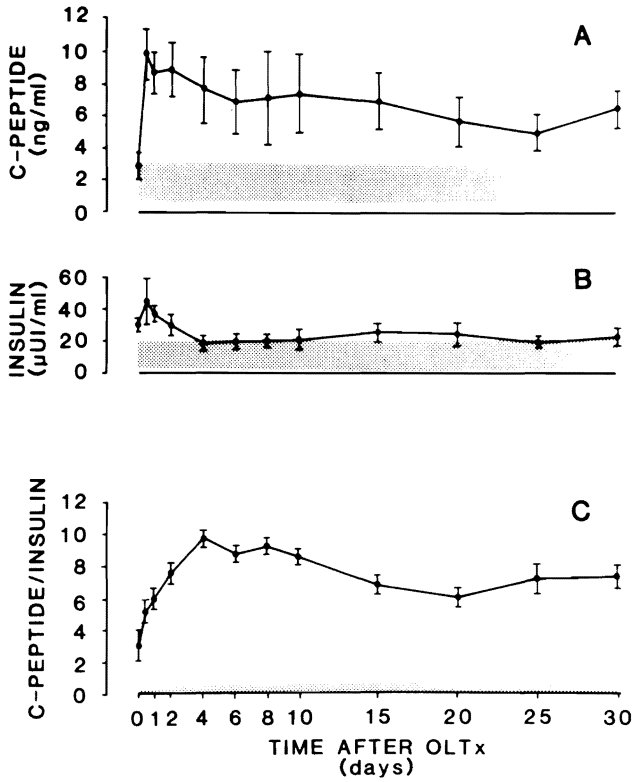

FIG. 1. Plasma C-peptide, insulin and C-peptide/insulin molar ratio levels in the eight patients before and after orthotopic liver transplantation (OLTx). The preoperative determinations were made at least 3 times in each patient. The *points* represent mean values. The *brackets* represent the S.D. All points after the zero in (A) except the 20- and 25-hr time points are different than the preoperative values, with a p value < 0.025. All points in (C) after time zero differ from those obtained preoperatively, with a p value of < 0.005.

The gel filtration studies demonstrated that the hyperglucagonemia, both before and after transplantation, was predominantly due to the presence of IRG having a molecular weight of 3,500 daltons. This form of the hormone is thought to be the most biologically active fraction (21). Figure 3 reports a sharp increase of plasma glucose levels probably related to the intense glucocorticoid therapy used during the first days following transplantation. Blood glucose levels returned to the normal range 6 days after operation and remained normal during all of the observation period.

Amino Acids: The preoperative elevations of AAAs (Figure 4C) and the depressed levels of BCAAs (Figure 4B) returned to the normal range for each within 12 hr after transplantation. More importantly, the plasma amino acid levels and the BCAA/AAA ratio (Figure 4A) subsequently achieved the normal range for the entire 30-day study period.

Control Study: No changes were observed in the normal levels of IRI, IRG and C-peptide levels following liver transplantation in the one patient with multiple hepatic adenomatosis studied (Figure 5A). Similarly, no changes were observed for these same substances in the five normal dogs submitted to liver transplantation (Figure 5B). However, this individual and these dogs had no abnormalities preoperatively that might otherwise have been expected to correct following successful transplantation. Importantly these data suggest that neither the doses of prednisone used nor the cyclosporine used to prevent rejection contributed to the hormonal and amino acid findings observed in the cirrhotic patients studied.

TABLE 4. Levels of glucagon, insulin, C-peptide and IRI/IRG molar ratio

	n	Total glucagon (pg/ml)	Glucagon (pg/ml)	Insulin (μU/ml)	C-Peptide (ng/ml)	IRI/IRG
Normal subjects	10	90 ± 15	75 ± 16	20 ± 5	3.2 ± 0.5	3.3 ± 0.3
Cirrhotic patients						
Before OLTx	8	350 ± 60 $p < 0.05$	294 ± 51 $p < 0.05$	25 ± 5 NS	4 ± 0.5 NS	1.5 ± 0.5 $p < 0.01$
30 days after OLTx	8	750 ± 110 $p < 0.01$	638 ± 87 $p < 0.01$	22 ± 8 NS	6 ± 1 $p < 0.01$	0.6 ± 0.1 $p < 0.001$
180 days after OLTx	8	80 ± 12 NS	68 ± 9 NS	30 ± 7.15 $p < 0.05$	3.8 ± 0.5 NS	10.2 ± 1 $p < 0.001$

Levels of glucagon, C-peptide, insulin and IRI/IRG ratio in normal subjects, and in eight cirrhotic patients who underwent liver transplantation. The determinations in the operated patients were made before transplantation, 30 days and 180 days after transplantation. The data for "normal subjects" refer to determinations obtained in 10 healthy people age 18 to 45 yr. Each value is expressed as mean ± S.D. Significance (p) is in relation to the values of normal subjects. Molecular weight of glucagon was 3,500 daltons. OLTx = orthotopic liver transplantation; NS = not statistically significant.

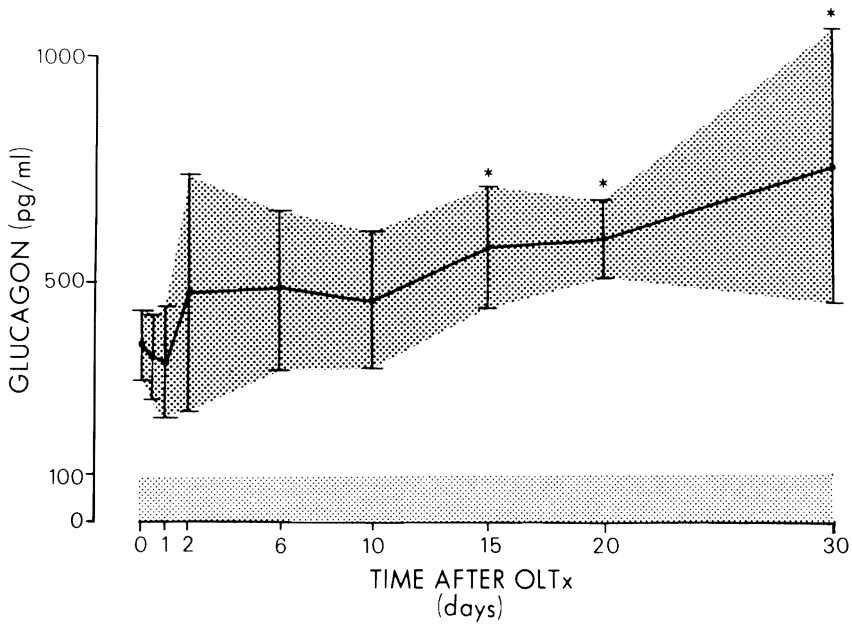

FIG. 2. Plasma glucagon in the eight patients before and after orthotopic liver transplantation (OLTx). Each value is expressed as mean ± S.D. *Asterisk* denotes a $p < 0.05$ value compared to the value determined preoperatively.

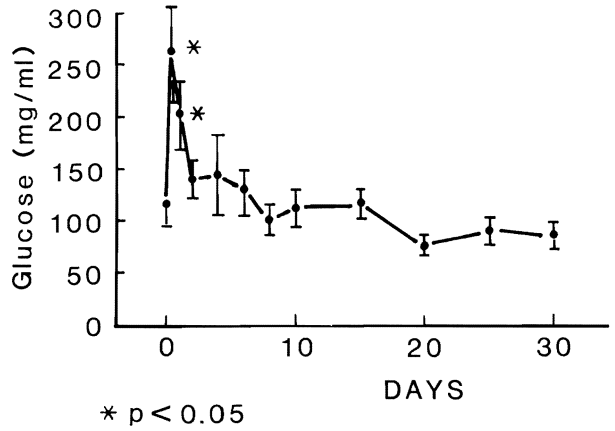

FIG. 3. Plasma glucose in the eight patients before and after orthotopic liver transplantation. Each value is expressed as mean ± S.D. *Asterisk* denotes a $p < 0.05$ value for the level denoted as compared to the preoperatively determined level.

DISCUSSION

The purpose of this study was to determine if the hormonal abnormalities which are characteristic of end-stage chronic liver disease can be corrected by orthotopic liver transplantation, and if so, how quickly. The evidence that has emerged is both conclusive and provocative. Both the hyperinsulinemia and the hyperglucagonemia evident preoperatively persisted for some time after successful transplantation, suggesting that the hypersecretion of these two hormones which characterizes chronic liver disease was not promptly corrected with elimination of the liver disease *per se*. Although the plasma insulin level gradually returned to the normal range within several days of the transplant procedure, the plasma glucagon level continued to be abnormally elevated and in fact became progressively more abnormal (more elevated) for several weeks before it also became normal sometime between 1 and 6 months postoperatively. These data, coupled with the data obtained from a patient with multiple hepatic adenoma but normal liver function, suggest that the abnormalities seen in the patients with advanced liver disease reflected alterations in hormone balance and energy metabolism, which were due to the individual's advanced liver disease and not to the surgical procedure and the immunotherapy that followed the procedure. These observations also support the prior findings of Sherwin et al. (7, 8) and Dudley et al. (21) that suggest that overproduction of the pancreatic hormones rather than defective hepatic uptake accounts for the hyperglucagonemia and hyperinsulinemia of advanced liver disease. Even more importantly, failure to demonstrate any relationship between the changes in the plasma levels of glucagon and either the BCAAs or AAAs in these studies suggests that the abnormal plasma levels of both classes of amino acids present in patients with liver disease are not regulated or determined to a major degree by the hyperglucagonemia present in patients with advanced liver disease. Conversely, these data suggest that the elevated plasma levels of glucagon seen in advanced liver disease play little or no role in the production or maintenance of the abnormal plasma amino acid levels seen in patients with advanced liver disease.

The rather abrupt increases observed in plasma glucagon levels and insulin secretion documented by the increased C-peptide levels observed in the early postoperative period may represent homeostatic regenerative signals associated with or due to the transplantation procedure *per se* and the expected loss of hepatocytes that occurs due to unavoidable graft ischemia (occurring during organ harvesting) and mild to moderate rejection that are also a consequence of the procedure.

In contrast to the observations for plasma glucagon, plasma insulin levels returned to near-normal range within days of the transplant procedure, despite apparent persistent hypersecretion of the hormone documented by the increased plasma level of C-peptide and a progressive rise in the C-peptide/insulin ratio. This apparent increase in insulin secretion was independent of the tran-

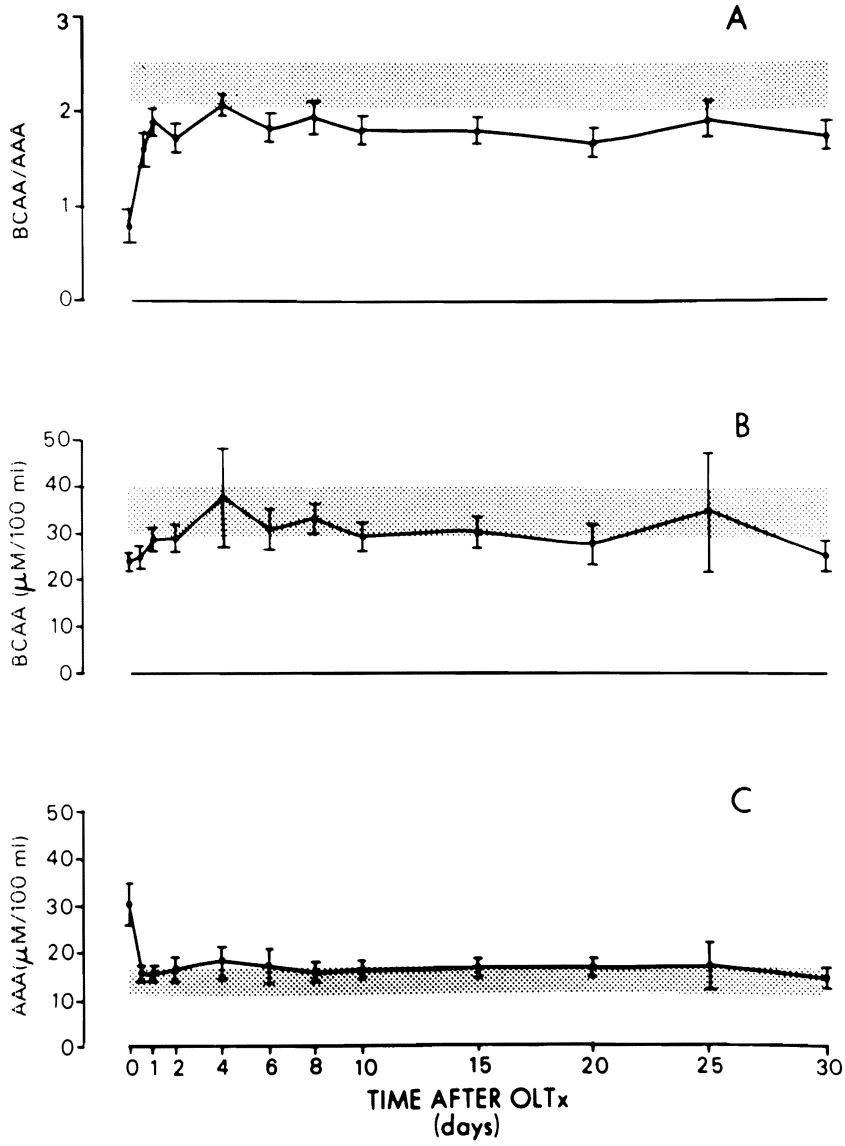

FIG. 4. BCAA/AAA molar ratio and BCAA and AAA levels in the eight patients before and after orthotopic liver transplantation (OLTx). The preoperative determinations were made at least 3 times in each patient. Each value is expressed as mean ± S.D. The *shaded area* represents the range of values for normal individuals.

sient increase of glucose observed during the first 6 days after transplantation and is well beyond the period of increased blood glucose seen postoperatively. These data suggest that the transplanted liver actively removes secreted insulin from the portal circulation, thereby maintaining a normal systemic plasma level of the hormone despite excess production and secretion of the hormone by the pancreas. It should be noted, however, that several recent studies have suggested that cyclosporine inhibits insulin synthesis and secretion by the pancreas (22–24). Moreover, as the renal function of the patients and the animals studied did not become impaired (data not shown), it is most unlikely that these changes reflect an alteration in renal handling or clearance of either C-peptide or insulin. Nonetheless, it is at least theoretically possible that the increased C-peptide levels reflect cyclosporine nephrotoxicity not apparent from the serial creatinine or blood urea nitrogen determinations made throughout the study.

The changes in the plasma levels of insulin and glucagon seen in the eight patients with advanced chronic liver disease, who were studied, were not seen in the one patient with normal hepatic function and multiple hepatic adenomatosis studied or in the five normal dogs that were transplanted experimentally. Thus, the hormonal changes observed in the patients with advanced liver disease would appear to be specific for liver disease *per se* and not the transplant procedure or the immunosuppressive regimen used.

Relevant to this point, it should be remembered that, as a direct consequence of the liver transplantation procedure for endstage liver disease, that the portosystemic collaterals that have developed between the viscera and the systemic circulation, as a result of the associated portal hypertension present in such patients preoperatively, are destroyed. Such shunts have been suggested to be the route by which plasma glucagon levels are increased in patients with advanced liver disease (7, 19). Our data would provide rather strong support against such a possibility, in that following the destruction of most, if not all, of these shunts during the operative procedure, the systemic plasma level of glucagon in-

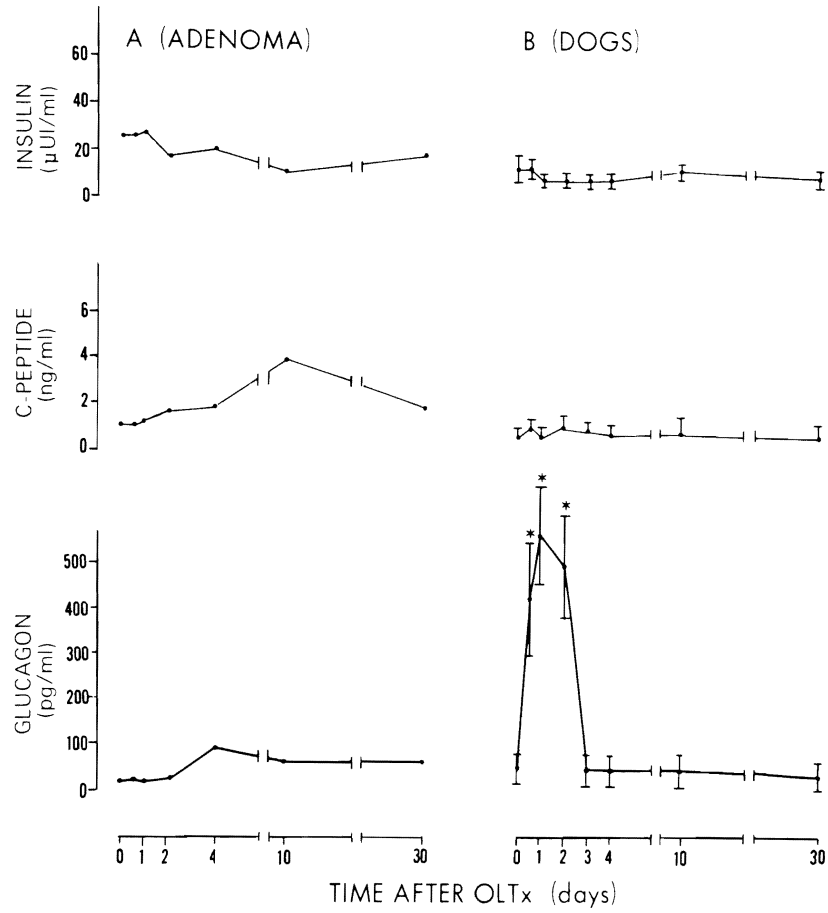

FIG. 5. Insulin, C-peptide and glucagon levels in a noncirrhotic patient who received orthotopic liver transplantation (OLTx) for multiple hepatic adenomas (A) and in five normal dogs before and after liver replacement (B). Each value is expressed as mean ± S.D. *Asterisk* denotes a $p < 0.05$ value as compared to the value observed preoperatively.

creased even further. In contrast, the present data suggest, but do not prove, that hypersecretion and not hepatic circulatory bypass via collateral vessels accounts for the hyperglucagonemia seen in cases of advanced chronic liver disease.

Furthermore, in contrast to current popular opinion which suggests that the hyperglucagonemia of chronic liver disease accounts for the reduced plasma levels of the BCAAs relative to those for the AAAs seen in individuals with liver disease, the present data suggest that such is not the case. Specifically, despite persistent and, in fact, worsening hyperglucagonemia, the plasma amino acid levels rapidly returned to normal following successful transplantation. This normalization of the plasma amino acid levels was similar to, and occurred in concert with, the changes observed for plasma insulin. These data are consistent with the recent suggestion that the reduced BCAA levels seen in cases of advanced cirrhosis are due to the increased plasma levels of insulin seen in such individuals. It has been proposed by the authors of this latter hypothesis that the systemic hyperinsulinemia of advanced chronic liver disease drives plasma BCAA into adipocytes, thereby producing an abnormal reduction in the plasma level of the BCAAs, which is characteristic of cirrhosis (13). The current observations that the plasma levels of the BCAAs normalize concurrently with the plasma levels of insulin provides strong, albeit indirect, support for this hypothesis. Equally important, however, is the observation that the plasma level of BCAAs normalize while the plasma glucagon level becomes progressively more abnormal. This suggests that the plasma levels of glucagon do not regulate the plasma level of the BCAAs.

Many investigators have reported reduced insulin sensitivity in cirrhotics being defined in terms of the observed reduction in plasma glucose and glucose utilization as well as reduced plasma levels of BCAAs in response to exogenous insulin infusions (26–29). It is of some interest that similar results have been obtained under conditions of euglycemia and uncontrolled glucose concentrations. Although these data clearly demonstrate end organ hyporesponsiveness to insulin, they by no means demonstrate that insulin alone regulates the plasma concentration of the BCAAs in either normal or cirrhotic individuals. Specifically, they demonstrate just the opposite; i.e., although insulin exerts some control over the plasma level of BCAAs as a result of its ability to enhance BCAA entry into muscle, this control has only a moderate effect at best upon the measured plasma level of the BCAAs (28).

In contrast to the complex factors that appear to control the plasma levels of the BCAAs, the changes observed in the AAAs in patients with liver disease are more clearly explained as being due solely to a reduced hepatic clearance of these amino acids (30). With replacement of the diseased liver with a normal liver, the plasma level of the AAAs returns to normal.

Finally, the present study demonstrates that studies such as this can provide important insight, not otherwise obtainable, to a better understanding of some of the

metabolic abnormalities that accompany chronic advanced liver disease. It also needs to be stated, however, that any attempt to correlate the blood levels of different metabolic substances is precarious and that any such relationship, when found, need not be causal. Nonetheless, these data suggest that, by monitoring the plasma levels of certain hormones, particularly insulin, and the plasma levels of various amino acids, and the ratio of the BCAAs to the AAAs, information concerning graft function in the very early postoperative period can be obtained which can be used by transplant surgeons when the more usually obtained parameters of hepatic injury and/or function are more difficult to interpret, as a consequence of the transplant procedure itself. Early reports confirming this suggestion have already been reported by Reilly et al. (31), Fath et al. (32) and Pearly et al. (33).

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