Effects of Chronic Glucagon Excess on Hepatic Metabolism

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SUMMARY

To investigate the effect of chronic hyperglucagonemia on hepatic metabolism, we have studied net splanchnic glucose and ketone body production rates in a patient with glucagonoma before and after complete tumor resection. Preoperatively, immunoreactive glucagon (IRG) concentration was high (1,800 pg. per milliliter) and the molar insulin/glucagon (I/G) ratio was low (0.4). Arterial free fatty acid (FFA) concentration (0.74 mM) and net splanchnic FFA uptake (0.27 mmole per minute) were normal. However, 48 per cent of the net splanchnic FFA uptake was utilized for net splanchnic ketone body production, which was four times (0.52 mmole per minute) greater than normal. Postoperatively IRG (40 to 150 pg. per milliliter) and the molar I/G ratio (> 1.0) were both normal. Arterial FFA concentration and net splanchnic FFA uptake were unchanged (0.67 mM and 0.27 mmole per minute, respectively). However, only 19 per cent of the net splanchnic FFA uptake was utilized for net splanchnic ketone body production, which had declined to 0.19 mmole per minute. These data suggest that chronic hyperglucagonemia in this patient had a stimulating effect on ketogenesis.

Preoperatively, the net splanchnic glucose production rate was 0.56 mmole per minute and could be accounted for entirely by gluconeogenesis from lactate (83 per cent), pyruvate (9 per cent), glycerol (14 per cent), and alanine, glutamine, and glutamate (8 per cent). The abnormally large contribution of lactate to gluconeogenesis was an effect of inappropriately elevated lactate concentration (0.88 mM) and increased blood flow (2,400 ml. per minute). Postoperatively the net splanchnic glucose production rate was 0.67 mmole per minute, of which 51 per cent could be accounted for by gluconeogenesis. The data provide no evidence for an effect of chronic hyperglucagonemia on splanchnic glucose production. However, they do not exclude a small stimulating glucagon effect on gluconeogenesis from amino acids. DIABETES *27*:643-48, June, 1978.

The role of glucagon in normal human physiology and in diabetes is of great interest but remains uncertain. Results obtained in the past with pharmacologic doses of glucagon are of questionable significance. Recently somatostatin has been used by different investigators in an attempt to separate the action of glucagon from that of insulin on hepatic ketone body and glucose production. The data obtained suggest that glucagon plays a role in hepatic gluconeogenesis[1] and ketogenesis.[2] Somatostatin, however, not only suppresses a large number of hormones other than insulin and glucagon, but, in addition, has profound effects on splanchnic blood flow[1,2] and on intestinal digestive, absorptive, and motor functions.[3-5] Therefore, it is difficult to be certain that metabolic effects obtained with its use are solely due to either glucagon or insulin suppression. Furthermore, the effect of glucagon on hepatic metabolism has been studied only in acute experiments, while no data are available on chronic glucagon effects. Information on the latter, however, would be of considerable interest in view of the recent recognition that the glycogenolytic action of glucagon is of short duration[6] and also with respect to the postulated pathogenetic role of glucagon in diabetes.[7]

In the current study, we have investigated net splanchnic glucose and ketone body production rates in a patient with chronically elevated glucagon concentrations secondary to an islet cell carcinoma secreting excessive amounts of bioactive glucagon.[8] The patient was restudied after complete resection of the tumor and after glucagon concentrations had normalized. The data obtained suggested that chronic elevations of endogenous glucagon stimulated ketogenesis, whereas no effect on glucose production was demonstrable.

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MATERIALS AND METHODS

Patient. The clinical and biochemical manifesta-

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tions of the glucagonoma in this patient have been described in detail.[8] In brief, this 52-year-old Caucasian man had chronic dermatitis, mild adult-onset diabetes mellitus, severe weight loss, and anemia. After an overnight fast, his plasma immunoreactive glucagon (IRG) and immunoreactive insulin (IRI) concentrations were 1,800 pg. per milliliter and 60 μU. per milliliter, respectively. After resection of an islet cell carcinoma weighing 100 gm. through partial pancreatectomy, his plasma IRG and IRI concentrations returned to normal (40 to 150 pg. per milliliter and 10 to 12 μU. per milliliter, respectively) and his dermatitis cleared, he gained weight, and his anemia disappeared; his diabetic state, however, deteriorated. An insulinoma was found within the glucagonoma. Removal of this additional source for insulin was probably the cause for the patient's postoperative rise in blood sugar.

Catheterization, blood flow, and blood sampling. Catheterization studies were performed before resection of the tumor and again two months postoperatively. Dietary intake for one week before both procedures was the same and consisted of 2500 calories per day containing 150 gm. protein, 220 gm. carbohydrate, and 113 gm. fat. The patient did not receive insulin or any other medication for at least two weeks before each study. Catheterizations were performed as described previously.[9]

Chemical analysis. The methods used and the analytic precision for determining blood acetoacetate (AcAc), β-hydroxybutyrate (β-OHB), glycerol, lactate, pyruvate, glucose, alanine, glutamine, glutamate, and plasma triglycerides and free fatty acids (FFA) have been previously published.[9] Glucagon[10] and insulin[11] levels were determined by radioimmunoassay. Unger's 30 K antibody was used in the glucagon assay. Gel filtration studies for glucagon and insulin were performed as described previously.[12]

Calculations. Net splanchnic uptake and release rates of substrates were calculated by multiplying the arteriovenous concentration differences by the measured hepatic plasma flow rates or by the computed hepatic blood flow rates. Hepatic plasma flow rates were converted to hepatic blood flow rates by the formula: blood flow rate = plasma flow rate/ 1−hematocrit. Fractional extractions were calculated as follows: arteriovenous concentration difference/ arterial concentration.

RESULTS

Hormone fractionation: insulin/glucagon ratios. To evaluate possible metabolic effects of chronic hyperglucagonemia in this patient, the relationship of bioactive glucagon to bioactive insulin was estimated. Preoperatively, 64 per cent (1,150 pg. per milliliter) of this patient's basal IRG eluted with the glucagon marker (Mol. wt. 3,500) and, thus, can be considered to be fully bioactive.[13] The remaining 36 per cent (650 pg. per milliliter) eluted with the proinsulin marker (Mol. wt. 9,000). The bioactivity of this fraction has been reported to be about 30 per cent.[14] Basal IRI concentration was 60 μU. per milliliter. Of this, 20 μU. per milliliter eluted with the insulin marker (Mol. wt. 6,000) and, thus, can be considered to be fully bioactive. Another 20 μU. per milliliter eluted with the proinsulin marker. The bioactivity of this material has been reported to be very low (2 to 20 per cent, average about 10 per cent).[15] The remainder eluted within the void volume (big big insulin, Mol. wt. > 30,000) and had probably no bioactivity. The molar I/G ratio, considering only bioactive hormones, was about 0.4. Postoperatively, basal IRG concentration was 120 pg. per milliliter. Approximately equal amounts eluted with the glucagon (43 per cent) and the proinsulin (45 per cent) markers. A small amount of IRG (12 per cent) eluted within the void volume. Basal IRI concentration was 12 μU. per milliliter, and the I/G ratio had risen to greater than 1.0.*

Arterial concentration and splanchnic arteriovenous concentration differences (table 1). Preoperatively, the concentration of glucose was only slightly elevated (6.41 mM). Arterial AcAc and β-OHB concentrations (0.206 and 0.448 mM, respectively) were about four and eight times our overnight-fasting normal values, respectively.[17] Alanine and glutamine concentrations (0.110 and 0.154 mM, respectively) were depressed to about one-third their normal concentrations.[9] Glutamate concentration (0.128 mM) was normal.[9] There was a net splanchnic uptake of FFA, triglycerides, lactate, pyruvate, glycerol, alanine, and glutamine, and a net splanchnic production of AcAc, β-OHB, glucose, and glutamate. Fractional uptakes were 0.22 for FFA, 0.02 for triglycerides, 0.74 for glycerol, 0.44 for lactate, 0.53 for pyruvate, 0.31 for alanine, and 0.05 for glutamine.

*Postoperative insulin could not be fractionated due to lack of sufficient amounts of plasma. If pro- and big big insulin accounted for as much as 66 per cent of total insulin immunoreactivity (as was the case preoperatively), I/G would have been about 1.5. However, it is more likely that postoperatively pro- and big big insulin concentrations were normal and accounted for about 12 per cent of total insulin immunoreactivity.[16] In this case, I/G could have been as high as 3.5.

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TABLE 1

Arterial substrate concentrations, arteriohepatic venous concentration differences, hepatic blood and plasma flow rates, and splanchnic balance*

Substrates of Lipid Metabolism

	FFA†		TG†		AcAc		β-OHB	
	Arterial	A-HV	Arterial	A-HV	Arterial	A-HV	Arterial	A-HV
Pre-op	0.740	+0.165	0.992	+0.023	0.206	−0.103	0.448	−0.112
Post-op	0.666	+0.277	1.015	−0.049	0.128	−0.076	0.196	−0.062

Substrates of Carbohydrate Metabolism

	Glucose		Lactate		Pyruvate		Glycerol		Alanine		Glutamine		Glutamate	
	A	A-HV	A	A-HV	A	A-HV	A	A-HV	A	A-HV	A	A-HV	A	A-HV
Pre-op	6.411	−0.232	0.878	+0.384	0.080	+0.042	0.087	+0.064	0.110	+0.034	0.154	+0.007	0.128	−0.005
Post-op	12.673	−0.481	0.608	+0.324	0.076	+0.036	0.072	+0.039	0.298	+0.093	0.812	+0.080	0.285	−0.082

Hepatic Flow Rates

	Blood	Plasma
Pre-op	2,400 ml. per minute	1,630 ml. per minute
Post-op	1,400 ml. per minute	940 ml. per minute

Net Splanchnic Release and Uptake of Substrates

	FFA†	TG†	AcAc	β-OHB	Gluc	Lact	Pyru	Glyc	Ala	Gln	Glut
Pre-op	+0.269	+0.038	−0.247	−0.269	−0.557	+0.922	+0.101	+0.154	+0.082	+0.017	−0.012
Post-op	+0.260	−0.047	−0.106	−0.087	−0.673	+0.454	+0.050	+0.055	+0.130	+0.112	−0.115

Abbreviations: FFA, free fatty acids; TG, triglycerides; AcAc, acetoacetate; β-OHB, beta-hydroxybutyrate; Gluc, glucose; Lact, lactate; Pyru, pyruvate; Glyc, glycerol; Ala, alanine; Glu, glutamine; Glut, glutamate.

*Concentrations are given in mmoles per liter, substrate uptake (+) or release (−) represents the arterio-hepatic-venous (A-HV) concentration differences, and splanchnic balance data are given in mmoles per minute.

†Indicates plasma values.

Postoperatively, arterial concentrations of AcAc and β-OHB had decreased to 0.128 and 0.196 mM, respectively. These concentrations exceed normal concentrations but are depressed to about 50 per cent of the preoperative values. Alanine, glutamine, and glutamate concentrations rose to high normal values of 0.298, 0.812, and 0.285 mM, respectively. Glucose concentration rose to 12.673 mM. The small net triglyceride uptake seen before operation had changed to a small net splanchnic production. The fractional uptake for FFA increased from 0.22 to 0.42; that of lactate increased from 0.44 to 0.53; that of glycerol decreased from 0.74 to 0.54, while the fractional uptakes for pyruvate and alanine remained essentially unchanged.

Splanchnic production and utilization rates (table 1 and figure 1). Preoperatively, the splanchnic (hepatic) bed extracted 0.269 mmole per minute of FFA and 0.038 mmole per minute of triglycerides and produced 0.247 mmole per minute of AcAc and 0.269 mmole per minute of β-OHB. The splanchnic bed also extracted 0.922 mmole per minute of lactate and 0.101 mmole per minute of pyruvate, 0.154 mmole per minute of glycerol, and 0.082 mmole per minute of alanine and 0.017 mmole per minute of glutamine, and released 0.012 mmole per minute of glutamate; thus, net value of "α-ketoglutarate equivalents" was

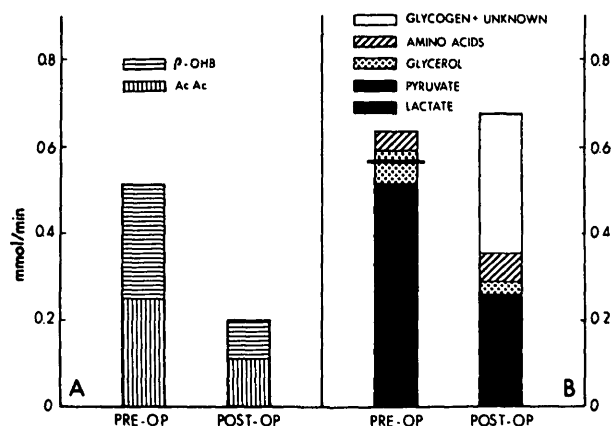

FIG. 1. (Left) Pre- and postoperative net splanchnic β-hydroxybutyrate and acetoacetate release. (Right) Pre- and postoperative net splanchnic glucose release and precursor uptake. Amino acids = the sum of alanine, glutamine, and glutamate uptake. The preoperative net splanchnic glucose release of 0.557 mmole per minute is indicated by a horizontal line (through glycerol uptake). Precursor uptake (assuming complete transformation into glucose) accounted for 113 per cent (0.631 mmole per minute) of measured glucose release.

0.005 mmole per minute.† Glucose production rate was 0.557 mmole per minute. Assuming that all extracted substrates were quantitatively converted into

†See footnote on page 389 of reference 9.

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glucose, it can be calculated that gluconeogenesis accounted for 113 per cent of the net splanchnic glucose output. It is noteworthy that uptake of lactate alone could account for 83 per cent of glucose production, while alanine uptake could contribute only 7 per cent.

Postoperatively, the splanchnic bed extracted the same amount of FFA (0.260 mmole per minute) as it did preoperatively. However, ketogenesis was reduced by 63 per cent (0.106 and 0.087 mmole per minute for AcAc and β-OHB, respectively). Compared with the preoperative extraction rates, uptake of lactate, pyruvate, and glycerol decreased by 51, 50, and 64 per cent, respectively, while alanine and glutamine uptake increased. However, there was a large release of glutamate resulting in a net loss of 0.003 mmole per minute of "α-ketoglutarate equivalents" for gluconeogenesis. Net splanchnic glucose uptake was 0.673 mmole per minute, and uptake of gluconeogenic precursors could account for about 51 per cent of this glucose production.

DISCUSSION

An important finding in this patient was the strong association between chronic hyperglucagonemia and ketogenesis. Preoperatively, when IRG concentration was high and the molar I/G ratio was low, net splanchnic ketone body production was increased about fourfold over that observed in normal man after an overnight fast. Postoperatively, after IRG concentration had normalized, the ketone body production rate declined to one-third the preoperative value despite a marked deterioration of the patient's diabetic state. These changes are not explained by changes of blood flow since the postoperative decrease in blood flow (from 2,400 ml. to 1,400 ml. per minute) could account for not more than 42 per cent of the fall in ketone body release. Furthermore, it is noteworthy that this diminution occurred despite an unchanged arterial concentration and an unchanged splanchnic uptake of FFA, which remained about 0.7 mM and 0.26 mmole per minute, respectively. Using palmitic acid as a model precursor for ketone body synthesis, it can be calculated that preoperatively about 48 per cent of the net splanchnic FFA uptake was utilized for synthesis of ketone bodies, whereas postoperatively only 19 per cent was used for this purpose.

There is much evidence to suggest that this patient's augmented ketogenesis was, in fact, caused by his chronic hyperglucagonemia. None of the other preoperatively existing abnormalities—high insulin, low amino acid concentration, or a tumor—is known to stimulate ketogenesis. The mild diabetic state cannot be incriminated since ketogenesis decreased postoperatively when the diabetic state had worsened considerably. Furthermore, our observations are in good agreement with results obtained by others. McGarry et al.[18] have demonstrated in rats that glucagon can transform the hepatic enzymatic profile in such a way that fatty acids are preferentially used for ketone body formation. Schade et al.[19] have shown in man that infusion of physiologic doses of glucagon are ketogenic in the acute experiment. Furthermore, Gerich et al.[20] were able to suppress ketogenesis in diabetic patients by inhibition of glucagon with somatostatin. Our data suggest that endogenous glucagon has a long-lasting effect on ketogenesis in contrast to its evanescent action on glycogenolysis.[6]

Furthermore, the data indicate that the effect is exclusively on the splanchnic (hepatic) bed since no signs of enhanced lipolysis were seen. The latter observation is in agreement with data of Lefebvre et al., who found in vitro that glucagon induced lipolysis only when the molar I/G ratio was 0.1 or less.[21]

Preoperatively, net splanchnic glucose production in this patient was 0.56 mmole per minute, which is below the value reported for overnight-fasted normal subjects.[22] In marked contrast to the normal situation, the entire glucose production could be accounted for by gluconeogenesis from lactate, pyruvate, glycerol, alanine, and α-ketoglutarate equivalents, while none of it appeared to be derived from glycogenolysis. The absence of a demonstrable stimulatory effect of chronic hyperglucagonemia on glycogenolysis after an overnight fast is compatible with a short-lasting effect of glucagon on glycogenolysis.[6] However, it is also possible that the mobilizable hepatic glycogen was already depleted during the night and before the catheterization study. The abnormally large contribution of lactate to gluconeogenesis (83 per cent) can best be explained by the greatly increased availability of this substrate, inasmuch as it has been shown that glucose output rises linearly with lactate supply.[23] The abnormally elevated supply of lactate was due to the heightened preoperative blood flow rate (2,400 ml. per minute) coupled with a lactate concentration that was inappropriately high for this blood flow. Postoperatively, splanchnic lactate uptake decreased concomitantly with the blood flow rate, whereas the fractional uptake of lactate remained unchanged. The origin for this lactate was not explored. It is likely that the large glucagonoma produced part of it. In this respect, in-

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creased Cori cycle activity has been found in patients with cancers.[24] The remainder of the lactate probably came from peripheral tissues, perhaps due to the inhibitory effect of ketone bodies on pyruvate oxidation.[25] The hypoaminoacidemia in this patient was probably a consequence of his hyperglucagonemia, since it appears to be a universal finding in patients with glucagonoma[26] and has been produced in man by infusing physiologic amounts of hormone.[27] The mechanism through which glucagon causes hypoaminoacidemia is less clear. It has been suggested that glucagon exerts a stimulatory effect on hepatic gluconeogenesis from amino acids, particularly from alanine.[28] Our failure to detect a preoperative increase in net splanchnic uptake of alanine, glutamine, and glutamate does not rule out a stimulatory effect of chronic hyperglucagonemia on gluconeogenesis from amino acids. In fact, Jennings et al. have recently demonstrated that small decreases in glucagon concentrations result in diminished gluconeogenesis from alanine without affecting alanine uptake by the liver.[29] Thus, our findings of marked increases in the arterial concentrations of alanine, glutamine, and glutamate postoperatively and the fact that the skin, blood cell, and muscle masses returned to normal suggest that glucagon has both chronic hepatic and extrahepatic actions on amino acid metabolism.

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