SHORT COMMUNICATIONS

The Behaviour of Insulinaemia in Patients with Liver Cirrhosis after Intravenous Administration of Glucose, Tolbutamide and Glucagon*

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Summary. The response of both blood glucose and serum immunoreactive insulin to glucagon, glucose and tolbutamide was studied in ten patients with well-documented, advanced liver cirrhosis and in ten healthy subjects without history indicative of liver impairment or diabetes. Glucose was administered as a rapid intravenous injection in a dose of 0.33 g/kg of body weight, tolbutamide in a dose of 1.0 g and glucagon in a dose of 1.0 mg. The mean fasting serum insulin levels of cirrhotic patients did not differ significantly from the values

obtained in healthy subjects. However, after administration of glucose or tolbutamide the rise of insulinaemia was significantly higher in cases of liver cirrhosis than in normal subjects. The increase of serum insulin values after intravenous administration of glucagon was similar in both groups; thus glucagon failed to induce hyperinsulinaemia as observed after glucose or tolbutamide. The possible causes of this phenomenon have been discussed.

In liver cirrhosis, the insulin level of the blood has been shown to increase upon stimulation of the islets' B-cell function by the administration of glucose and tolbutamide (Creutzfeld *et al.*, 1967; Magyesi *et al.*, 1967; Samaan *et al.*, 1968).

The present study concerns the behaviour of the insulin level of the blood in patients with liver cirrhosis after intravenous glucagon administration, as well as the comparison of this effect with the action of other stimuli enhancing the secretion and release of insulin, i.e. glucose and tolbutamide.

Material and Methods

The material comprised 10 patients with advanced liver cirrhosis, as well as 10 healthy subjects with no history indicative of diabetes or liver disease, and with normal hepatic function tests. Subjects with abnormal glucose tolerance or obesity were ruled out. The age of patients with liver cirrhosis was from 40 to 56, and that of healthy subjects was from 30 to 60 years. The group of patients included nine men and one woman; alcoholic cirrhosis of the liver was diagnosed in six cases, post-necrotic cirrhosis in three, and cirrhosis with an ill-defined aetiology in one. Nine patients showed hepatomegaly; eight, symptoms of portal hypertension; four, ascites; and four, jaundice (serum bilirubin level 1.8–7.2 mg %). In all cases, bromsulphthalein retention was increased, amounting to 15–40% in the 45th min of the test.

Glucose was administered as a rapid intravenous injection in a dose of 0.33 g/kg of body weight (Conard, 1955); tolbutamide, intravenously in a dose of 1.0 g; and glucagon, intravenously in a dose of 1.0 mg.

Blood glucose content was determined according to King and serum insulin level by the radioimmunological method (Melani *et al.*, 1965).

Results

In cases of liver cirrhosis, insulin level of the blood during fasting was either normal or slightly and insignificantly increased; on the other hand, the increase in insulinaemia after glucose administration was significantly greater in these patients, compared with healthy subjects (in 15th min, $p < 0.0025$; in 30th min, $p < 0.005$; in 60th min, $p < 0.01$). At the same time, the K-value was lower in the group of cirrhotic patients ($K = 1.38 \pm 0.15 \times 10^{-2}$ mg/100 ml/min) than in controls ($K = 1.91 \pm 0.18 \times 10^{-2}$ mg/100 ml/min, $p < 0.05$) (Fig. 1).

After tolbutamide injection, the initial drop in glycaemia resembled that in the control group; at the later stage, the marked delay in the return of glycaemia to the initial values, characteristic of liver cirrhosis, was noticed (Fig. 2).

The rise of insulinaemia after tolbutamide administration was in the 15th min ($p < 0.005$) and 30th min ($p < 0.0025$) significantly higher in cases of liver cirrhosis than in normal subjects.

After glucagon administration, flattening of the glycaemia curve, characteristic of liver cirrhosis, was observed (Fig. 3). Blood insulin levels on fasting and

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Fig. 1. Blood glucose and serum insulin (IRI) levels after i.v. injection of glucose solution to healthy subjects and patients with liver cirrhosis

after glucagon injection were similar in both groups under comparison. Thus, in patients with liver cirrhosis, glucagon administration did not induce as great a hyperinsulinaemia as that observed after injection of glucose or tolbutamide. Consequently, the difference between the increase in insulinaemia after glucose or tolbutamide, on the one hand, and that after glucagon on the other, was greater in cases of liver cirrhosis than in healthy subjects. The values of insulinaemia and glycaemia observed after intravenous injection of all three stimuli are recorded in Tables 1 and 2.

Discussion

The phenomenon of hyperinsulinaemia exhibited by cases of liver cirrhosis can be explained by reduced sensitivity to insulin in this disease (Boller and Überack, 1932; Creutzfeldt, 1959, Creutzfeldt *et al.*, 1970, Czyżyk *et al.*, 1970). However, so far we are unable to account satisfactorily for the fact that glucagon-in-

Fig. 2. Blood glucose and serum insulin (IRI) levels after i.v. injection of sodium tolbutamide to healthy subjects and patients with liver cirrhosis

Fig. 3. Blood glucose and serum insulin (IRI) levels after i.v. injection of glucagon to healthy subjects and patients with liver cirrhosis

duced hyperinsulinaemia is of lower intensity than that due to administration of glucose or tolbutamide. Our results confirm the single observation of Marks and Samols (1968).

mols, 1968), it can be assumed that the reduction of glycogen stores in the cirrhotic liver can be the factor determining the secretory response of the B-cells to glucagon, as observed in this disease. Thus, the as-

Table 1. *The mean levels ($\pm$ S.E.) of blood glucose (mg/100 ml) and serum insulin levels (μ U/ml) in healthy subjects after i.v. administration of glucose, tolbutamide and glucagon*

Stimulus	0	2-3'	10'	15'	20'	30'	40'	50'	60'	
Glucose 0.33 g/kg i.v.	89 $\pm$ 10 16 $\pm$ 3	230 $\pm$ 43 74 $\pm$ 13	191 $\pm$ 47 —	177 $\pm$ 21 35 $\pm$ 5	155 $\pm$ 39 —	145 $\pm$ 22 26 $\pm$ 3	106 $\pm$ 28 —	92 $\pm$ 25 —	87 $\pm$ 20 21 $\pm$ 3	Blood glucose Serum IRI
Tolbutamide sodium 1.0 g i.v.	92 $\pm$ 11 15 $\pm$ 3	84 $\pm$ 11 76 $\pm$ 9	— —	— 40 $\pm$ 6	68 $\pm$ 15 —	64 $\pm$ 9 22 $\pm$ 5	47 $\pm$ 15 —	— —	62 $\pm$ 8 17 $\pm$ 3	Blood glucose Serum IRI
Glucagon 1 mg i.v.	84 $\pm$ 11 15 $\pm$ 3	91 $\pm$ 11 49 $\pm$ 9	107 $\pm$ 32 —	116 $\pm$ 18 31 $\pm$ 5	134 $\pm$ 24 —	120 $\pm$ 22 23 $\pm$ 4	102 $\pm$ 30 —	93 $\pm$ 31 —	87 $\pm$ 18 13 $\pm$ 3	Blood glucose Serum IRI

Table 2. *The mean levels ($\pm$ S.E.) of blood glucose (mg/100 ml) and serum insulin levels (μ U/ml) in patients with liver cirrhosis after i.v. administration of glucose, tolbutamide and glucagon*

Stimulus	0	2-3'	10'	15'	20'	30'	40'	50'	60'	
Glucose i.v. 0.33 g/kg	79 $\pm$ 10 14 $\pm$ 4	221 $\pm$ 31 85 $\pm$ 12	181 $\pm$ 29 —	— 60 $\pm$ 9	158 $\pm$ 19 —	135 $\pm$ 17 42 $\pm$ 7	120 $\pm$ 19 —	106 $\pm$ 17 —	96 $\pm$ 13 35 $\pm$ 6	Blood glucose Serum IRI
Tolbutamide sodium 1.0 g i.v.	78 $\pm$ 9 23 $\pm$ 3	75 $\pm$ 10 96 $\pm$ 20	— —	— 62 $\pm$ 11	65 $\pm$ 9 —	58 $\pm$ 8 50 $\pm$ 9	49 $\pm$ 8 —	— —	50 $\pm$ 8 20 $\pm$ 3	Blood glucose Serum IRI
Glucagon 1.0 mg i.v.	84 $\pm$ 10 17 $\pm$ 4	89 $\pm$ 10 49 $\pm$ 8	88 $\pm$ 15 —	— 35 $\pm$ 6	101 $\pm$ 12 —	97 $\pm$ 11 26 $\pm$ 6	90 $\pm$ 17 —	81 $\pm$ 13 —	80 $\pm$ 9 17 $\pm$ 4	Blood glucose Serum IRI

There is good evidence that glucagon promotes insulin secretion through an effect on adenylyl cyclase, bringing about an increase in cyclic-AMP (c-AMP) content in the B-cells (Turtle and Kipnis 1967; Malaisse, 1969). In turn, c-AMP is presumed to cause the release of insulin by exerting an effect on the hypothetical insulin-releasing unit (Cerasi and Luft 1970, Randle and Ashcroft, 1970). At the same time, c-AMP can affect insulin secretion via an effect on the metabolism of glucose in the B-cells; this assertion is supported by some observations indicating that the release of insulin indispensably requires the presence of metabolic intermediates located beyond the level 3-phosphoglyceraldehyde or even beyond the level of pyruvate (Lambert *et al.*, 1970), and that the insulin-releasing effect of glucagon increases with the rise of glucose concentration in the medium (Malaisse 1969). On the other hand, however, there is evidence that glucagon induces an only small decrease in the glycogen content of the islet cells (Hellman and Idahl, 1969), has no significant effect on the net glucose metabolism by both the pentose and Krebs cycles (Hostetler and Hollis, 1970), and promotes a significant, though small secretion of insulin in the absence of glucose in the medium (Lambert *et al.*, 1970). In conformity with the observation that the effect of glucagon on the secretion of insulin is related to the possibility of glucose utilization, and that the secretory response of the B-cells to glucagon administration is decreased in states proceeding with glycogen depletion (Marks and Sa-

sumption that the decreased effect of c-AMP in the B-cells results from too small a rise of glycaemia after glucagon loading, would be the simplest explanation of the insufficiently high increase in insulinaemia after glucagon administration in liver cirrhosis. It is stressed, however, that the increase in insulinaemia preceded the rise of glycaemia after glucagon injection.

Consequently, in the explanation of the difference between the promoting effect of glucose and tolbutamide on insulin secretion, on the one hand, and that of glucagon, on insulin secretion on the other, the part played by other factors possibly involved in liver cirrhosis cannot be ruled out; these factors include the reduced reactivity of adenylyl cyclase to glucagon, decreased adenylyl cyclase content in the B-cells or reduced sensitivity of the insulin-releasing unit to c-AMP.

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