The Release and Metabolism of Pancreatic Hormones After Major Hepatectomy in the Dog*

TAKEHARU ITATSU1, TAKEHIKO KISHIMOTO2, TSUYOSHI SHINTANI2, AND MITSUO UKAI3

1First Department of Internal Medicine, 2Second Department of Surgery and 3Institute of Germfree Life Research, Nagoya University School of Medicine, Nagoya 466, Japan

Synopsis

Major hepatectomy in the dog induced a 50% decrease in peripheral serum glucose, a 11-fold increase in portal plasma glucagon and a 36-fold increase in the portal glucagon/insulin ratio 3 hr after operation. Peripheral serum glucose levels were inversely correlated to the logarithmic value of portal plasma glucagon (r = −0.50, p < 0.01) and that of the portal glucagon/insulin ratio (r = −0.85, p < 0.01) for 1-6 hr after operation. The ratio of peripheral to portal plasma glucagon was also inversely correlated to the logarithmic value of portal plasma glucagon (r = −0.59, p < 0.01). In case of glucose infusion, plasma glucagon levels were not elevated after major hepatectomy.

The data suggest that glucose deficiency after major hepatectomy in the dog may cause hyperglucagonemia with an enhanced glucagon requirement.

The hypoglycemia after widespread removal of the liver has been demonstrated in rats (Weinbren et al., 1972; Wood et al., 1973) and humans (McDermott et al., 1963; Blumgart et al., 1972). In systemic blood of rats (Leffert et al., 1975), such effect was found to be associated with high glucagon and low insulin levels. In rats, other reports have not provided us with sufficient information to understand the nature of hepatectomy-induced hyperglucagonemia (Leffert et al., 1976) and hypoinsulinemia (Bucher et al., 1975).

The present work was undertaken to investigate two aspects (release and metabolism) of pancreatic hormones after major hepatectomy in the dog. For this purpose, the portal glucagon, insulin and glucagon/insulin ratio and the portal-peripheral vein gradient of these hormones were evaluated in relation to blood glucose levels.

Materials and Methods

After an overnight fast, female dogs weighing 10–15 kg were laparotomized under intravenous pentobarbital anesthesia in a supine posture. A polyethylene catheter was inserted into the portal vein and two catheters into the femoral veins.

The procedure of major hepatectomy began with clamping the left hepatic branches of portal vein and hepatic artery (at time zero) and finished with closing the abdominal wall (at 30 min). This operation resulted in removal of 71 ± 3 (Mean ± SD) % of the total liver. An infusion of physiological saline or 10% glucose (1 g/kg/hr) was made through a femoral catheter during the period of −0.5 to 6 hr. The rate of saline infusion was accelerated in the initial 1.5 hr to prevent blood loss due to surgical procedures and thereafter maintained at 10 ml/kg/hr.

Blood samples were obtained simultaneously through the portal and femoral vein catheters at the

Received April 12, 1978.

* Reprint requests should be addressed to M. Ukai, M.D., Institute of Germfree Life Research, Nagoya University School of Medicine, Showa-ku, Nagoya 466, Japan.
times indicated in the results. For glucagon and insulin assays, 2 ml blood samples were collected into tubes containing 1000 U Trasylol (Bayer Ltd.) and 2.4 mg of disodium ethylenediamine-tetraacetic acid.

Plasma insulin (IRI) and glucagon (IRG) were radioimmunoassayed by the solid phase method (Wide et al., 1966) and the use of Unger's 30K antibody (Böttger et al., 1973), respectively. Serum glucose and liver glycogen concentrations were determined by the glucose oxidase method (Bergmeyer et al., 1965) and anthron's method (Dreywood., 1946), respectively. The portal blood flow was measured with the electromagnetic flow meter (Narco Biosystems Inc., U.S.A.).

Statistical analysis was performed with the Student's t test, the criterion of significant difference being p<0.05 (Hill, 1967).

Results

In the dogs with saline infused (Fig. 1), major hepatectomy induced a 50\% decrease in peripheral serum glucose from 97 (mean value at time zero) to 48 mg/100 ml, an 11-fold increase in portal plasma IRG from 85 to 963 pg/ml (from 24 to 275 fmol/ml) and a decrease in portal plasma insulin from 0.68 to 0.20 ng/ml (from 118 to 37 fmol/ml) at 3 hr. The liver glycogen concentrations at zero and 6 hr were 24±8 and 2±1 (Mean±SD) mg/g liver, respectively. The portal blood flow in a dog fell from 382 ml/min (at time zero) to 192 ml/min (at 3 hr).

There was an inverse proportionality between the logarithmic value of portal plasma IRG and the peripheral serum glucose (r=−0.50, p<0.01) (Fig. 2, left). The better correlation (r=−0.85, p<0.01) was obtained between the logarithmic value of portal plasma IRG/IRI ratio and the peripheral serum glucose (Fig. 2, right).

The ratio of peripheral to portal plasma IRG was correlated to the logarithmic value of portal plasma IRG (r=−0.59, p<0.01), as shown in Fig. 3. However, the correlation between this ratio and the peripheral serum glucose and that between this ratio and the logarithmic value of portal plasma IRG/IRI ratio were not significant (Fig. 4).

In the dogs with glucose infused (Table 1), the peripheral serum glucose and the portal plasma insulin and glucagon at time zero (mean values) were 213 mg/100 ml, 2.16 ng/ml (54 μU/ml) and 25 pg/ml, respectively. Higher levels of peripheral serum glucose and portal plasma IRI and lower levels of portal plasma IRG were observed at 3 hr in these dogs in contrast to those in the dogs with saline infused.

![Fig. 1. Effect of major hepatectomy (0–30 min) on peripheral serum glucose and portal plasma IRG and IRI levels in 4 dogs. Values are Mean±SE. Significant differences from the time zero values are shown as p<0.05 (*), p<0.01 (**) and p<0.001 (**). The time zero values represent means of three or more preoperative values in all dogs.](image-url)
Fig. 2. The relation of the logarithmic values of portal plasma IRG (pg/ml in left panel; \( r = -0.50, p < 0.01, Y = -0.009X + 3.215 \)) or IRG/IRI ratio (pg/μU in right panel; \( r = -0.85, p < 0.01, Y = -0.022X + 3.212 \)) to peripheral serum glucose levels for 1–6 hr after major hepatectomy.

Fig. 3. The relation of the ratio of peripheral to portal plasma IRG to the logarithmic values of portal plasma IRG (pg/ml) for 1–6 hr after major hepatectomy. \( r = -0.59, p < 0.01, Y = -25.2X + 113.9 \).

Fig. 4. The relation of the ratio of peripheral (PE) to portal (PO) plasma IRG to other variables after major hepatectomy. Values are shown as their correlation coefficients. Significant differences are indicated by * \( (p < 0.01) \).
Table 1. Effect of glucose infusion (1 g/kg/hr) on peripheral (PE) serum glucose and portal (PO) plasma IRG and IRI levels after major hepatectomy

<table>
<thead>
<tr>
<th>Infusion</th>
<th>0</th>
<th>Time (hr)</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE-glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mg/100 ml)</td>
<td>saline</td>
<td>97±11</td>
<td>48±6</td>
</tr>
<tr>
<td></td>
<td>glucose</td>
<td>213±19***</td>
<td>407±85**</td>
</tr>
<tr>
<td>PO-IRI (ng/ml)</td>
<td>saline</td>
<td>0.68±0.24</td>
<td>0.20±0.04</td>
</tr>
<tr>
<td></td>
<td>glucose</td>
<td>2.16±0.52*</td>
<td>4.84±0.60***</td>
</tr>
<tr>
<td>PO-IRG (pg/ml)</td>
<td>saline</td>
<td>85±29</td>
<td>963±183</td>
</tr>
<tr>
<td></td>
<td>glucose</td>
<td>25±8</td>
<td>34±7***</td>
</tr>
<tr>
<td>PO-IRG/PO-IRI (molar ratio)</td>
<td>saline</td>
<td>0.212±0.084</td>
<td>7.685±0.819</td>
</tr>
<tr>
<td></td>
<td>glucose</td>
<td>0.022±0.007</td>
<td>0.012±0.003***</td>
</tr>
</tbody>
</table>

Each group consisted of 4 dogs. Values are Means±SE. Significant differences from the saline group are shown as p<0.05 (*), p<0.02 (**) and p<0.01 (**). The time zero values represent means of three or more preoperative values in all dogs with saline or glucose infusion. Postoperative values 3 and 6 hr after the initial procedure of major hepatectomy are shown.

The liver glycogen concentration was not reduced after major hepatectomy in the glucose group, as shown by 30±9 (mean±SD, at time zero) and 39±19 (at 6 hr) mg/g liver. The molar ratio of plasma IRG and IRI in the portal vein increased 36 fold from 0.21 to 7.69 at 3 hr in the saline group, while in the glucose group it decreased from 0.022 to 0.012 at 3 hr (Table 1).

Discussion

The role of the liver in carbohydrate homeostasis and metabolism of pancreatic hormones has occupied increasing attention in recent years. Aronsen et al. (1969) failed to find any significant changes in systemic blood glucose levels after 50% partial hepatectomy in the dog. In our laboratory, a 60% resection of the liver in a dog with saline infused resulted in a negligible change (104 to 99 mg/100 ml) in peripheral serum glucose levels, being associated with a mild rise (peak value 380 pg/ml) in portal plasma glucagon, while a 80% removal of the liver resulted in a striking fall from 91 to 24 mg/100 ml in systemic serum glucose with a rise of more than 1000 pg/ml in portal plasma glucagon.

These data favor the view that the fall in blood glucose levels after partial hepatectomy may be related to the quantity of the remnant liver (McDermott et al., 1963). This may be interpreted as indicating that the postoperative blood glucose levels depend upon the size of carbohydrate pool and the binding capacity of glucagon and insulin in the remnant liver.

Possible explanations for the mechanism of the hepatectomy-induced hyperglucagonemia may include the fact that the pancreatic release of glucagon is stimulated in response to the postoperative hypoglycemia and that the hepatic trap of portal glucagon is reduced as a result of loss of hepatic glucagon receptors after major hepatectomy. The former explanation is more plausible than the latter, because all of the dogs with glucose infused, in which serum glucose levels were kept normal or higher throughout the experiment, showed no increase in portal plasma glucagon levels following hepatectomy in this study. On the other hand, the preoperative (time zero) levels of portal plasma glucagon and insulin were unexpectedly low. This may be partly explained by the high rate of saline infusion which could dilute portal plasma. In a dog with saline infused, we found a 50% reduction of portal blood flow 3 hr
after operation, suggesting that the amount of portal glucagon entering into the liver increased 4.7 fold (from 32.4 to 184.8 ng/min) while that of portal insulin decreased remarkably (from 259.7 to 38.4 ng/min) 3 hr after operation. These are consistent with the assumption that 70% hepatectomized liver accumulates and/or sequesters glucagon more efficiently than insulin in the rat (Leffert et al., 1976).

The importance of the portal glucagon/insulin or insulin/glucagon ratio as a determinant of hepatic glucose output has been demonstrated in dogs (Ukai et al., 1977) and humans (Marliss et al., 1970; Unger, 1972). According to the study in rats (Parrilla et al., 1974), a molar glucagon/insulin ratio of 8.5 had a half maximal effect on hepatic glycogenolysis. In addition, Camargo et al. (1971) observed the enhanced gluconeogenesis in the remnant liver after partial hepatectomy in the rat. Taking these findings into consideration, the glucagon/insulin ratio of 7.7 obtained in this study may be interpreted as playing a role in enhancing glycogenolysis and gluconeogenesis in the remnant liver.

The ratio of the peripheral to portal plasma IRG was approximately 72% before operation in the dog with saline infused in our study. This is compatible with the study (76%) of Felig et al. (1974) and higher than that (59%) of Blackard et al. (1974). This ratio decreased significantly after major hepatectomy (Fig. 3). This may be related to glucagon trap by the liver (Buchanan et al., 1968; Ansorge et al., 1971; Pohl et al., 1972; Leffert et al., 1976) or other organs (Lefebvre et al., 1974; 1976; Duckworth, 1974; 1976) after operation, which awaits further analysis. On the other hand, the ratio of the peripheral to portal plasma IRI was 65% before operation in the dog with glucose infused, which was not significantly affected postoperatively.

It is likely that the secretory response of pancreatic hormones to major hepatectomy in the dog may depend dominantly upon a decrease in blood glucose and that the glucagon requirement may be enhanced probably to prevent glucose deficiency after this operation.

Acknowledgements

The authors are indebted to Miss Keiko Okada for expert technical assistance, to the Imanaga Medical Research Foundation, Nagoya, Japan for generous financial support, and to Narco Biosystem Inc., U.S.A. for kind help in using the electromagnetic flowmeter.

References