REVISTA ESPAÑOLA DE FISIOLOGIA, 40, 381-384. 1984

CARTAS AL EDITOR

Interrelationship Between Glucose Infusions and the Hepatic Handling of Bilirubin*

Glucose may play an important role in plasma clearance and/or in the different steps of hepatic bilirubin transport: e.g. glucose infusions seem to increase biliary bilirubin secretion in ponies (2). In jaundiced neonates, glucose enhances their serum albumin binding capacity reserve and results in a favourable clinical outcome (9). The present study was designed to determine the pathways by which glucose might improve the handling of bilirubin by the liver.

Rabbits received no food for 24 h before experiments. Animals were anaesthetized with sodium pentobarbitone (30 mg × kg^{-1}, i.v.). After tracheotomy, catheters were inserted into a femoral vein and artery; the pylorus was tied off and following the introduction of a catheter into the duodenum, the cystic duct was ligated and a polyethylene tube inserted into the common bile duct. Rectal temperature was held at 38.5 ± 0.5° C. After an equilibrium period of 30 min, bile was collected in nine consecutive samples of 20 min. A solution of NaCl (154 mmol × l^{-1}, group I), or glucose (227 mmol × l^{-1}, group II) was then infused intravenously for 1 h at a rate of 10 ml. h^{-1}. Bile was collected in an additional 1 h postinfusion period. The samples were collected in darkness under ice, a small fraction was kept and the rest was reinfused into the duodenum. Blood samples of 0.5 ml each were taken at intervals of 20 min.

Bilirubin concentration was assessed in bile (7) and glucose levels in plasma and bile (12). Plasma and bile osmolality were determined in a vapour pressure osmometer. Free fatty acids (FFA) were measured in plasma (5). UDP-glucose (6), bilirubin (10), bilirubin UDP-glucuronyl transferase (EC 2.4.1.17) activity (1) and the hepatic concentration of glucose after hydrolysis of glycogen (12) were estimated on liver homogenates. Statistical significance was calculated by Student's *t* test.

Table I shows that the activity of UDP-glucuronyl transferase determined in the liver samples obtained at 60 min after glucose infusion (group II) was significantly higher than that of control animals (group I). The changes in the enzymatic activity were accompanied by significant increases in hepatic glucose and UDP-glucose and by a nonsignificant decrease in the hepatic concentration of bilirubin. The concentration and excretion of total bilirubin in bile of the

* This work was supported by the «Comisión Asesora de Investigación Científica y Técnica».

Table I. *Determinations on liver in rabbits infused with NaCl (Group I) or glucose (Group II).* Mean values ± 1 SD. In parenthesis number of animals is given. N. S. = no significative.

	Group I		Group II		
Glucose (μmol × g^{-1} liver)	112 ± 8	(3)	402 ± 13	(3)	$P < 0.001$
UDP-glucose (μmol × g^{-1} liver)	0.25 ± 0.09	(5)	0.87 ± 0.10	(6)	$P < 0.001$
Non conjugated bilirubin (μmol × g^{-1} liver)	0.14 ± 0.03	(4)	0.10 ± 0.04	(6)	N.S.
UDP glucuronyl transferase activity (μmol × g^{-1} liver × h^{-1})	0.21 ± 0.07	(4)	0.49 ± 0.15	(5)	$P < 0.02$

two experimental groups determined before infusion were practically identical, while values after infusion were significantly different, both in terms of concentration (58 ± 21, n = 5 and 105 ± 42, n = 6 μmol. l^{-1}; $p < 0.01$) and excretion (11.2 ± 4.4, n = 5 and 18.0 ± 8.6, n = 6 nmol g^{-1} liver h^{-1}; $p < 0.05$) in groups I and II respectively. Glucose concentration in plasma of group I rabbits increased nonsignificantly by 10 % during experiments, while the values in group II increased by 102 %. The bile glucose concentration did not show any significant variation in group I whereas the values in group II increased by 750 % (18.7 mg 100 ml^{-1} in the postinfusion hour). No significant changes were observed in plasma or bile osmolality or in the plasma or bile osmolality or in the plasma concentration of FFA (0.088 ± 0.015, n = 4 and 0.086 ± 0.012, n = 5 μmol l^{-1}) in both experimental groups.

cretion after glucose infusion could be attributed to a greater binding of the pigment to plasma albumin, due to alterations in the concentration of different endogenous substances that act as competitive ligands, such as FFA (9). This possibility has recently been rejected (11), and does not seem very likely, since no changes in the plasma concentrations of FFA could be observed in our study. Another alternative would be an increase in the serum bilirubin levels, as has been described in Gilbert's syndrome (3) and which in our case could be due to haemolysis subsequent to changes in plasma osmolality. However, no rise in serum bilirubin levels has been reported in ponies (2) nor in jaundiced neonates (9) and in our experiments no significant changes could be observed in osmolality, in which our findings agree with those of OSTREA *et al.* (9).

An increased UDP-glucuronyl transferase activity has been found after the infusion of UDP-glucose (8). In our study, not only did we find noticeable hyperactivity on ending the glucose infusion, but also, this was accompanied by increases in the hepatic levels of UDP-glucose and glucose and by nonsignificant falls in the hepatic concentration of bilirubin. Even though such findings are in agreement and point to certain definite trends, we may not differentiate with certainty whether one is really dealing with a direct effect on the enzyme or whether this is perhaps indirect, stemming from a higher concentration of conjugating cofactor (the most likely), and neither may we even refer to the biological role of such increased enzymatic activity, since in the basal conditions the rabbit, as our own results indicate, has an excess of conjugating activity. Finally, we do not believe that the greater excretion of bilirubin after glucose infusion is due to an unspecific effect on bile secretion, since not only

does this secretion not increase, but rather, it decreases, probably due to ductular reabsorption of glucose (4) and the consequent reabsorption of water.

Acknowledgements

This work was supported by the «Comisión Asesora de Investigación Científica y Técnica», Spain.

References

1. BELLET, H. and RAYNAUD, A.: *Clin. Chim. Acta*, 53, 51-55, 1974.
2. CANNING, J. F.: *Q. Jl. exp. Physiol.*, 67, 311-321, 1982.
3. GOLLAN, J. L., BATEMAN, C. and BILLING, B. H.: *Gut*, 17, 335-340, 1976.
4. GUZELIAN, P. and BOYER, J. L.: *J. Clin. Invest.*, 53, 526-535, 1974.
5. ITAYA, K. and VI, M.: *J. Lipid. Res.*, 6, 16-20, 1965.
6. KEPLER, D. and DECKER, K.: *Eur. J. Biochem.*, 10, 219-225, 1969.
7. MALLOY, H. T. and EVELYN, K. A.: *J. Biol. Chem.*, 119, 481-487, 1937.
8. OKOLICKSANYI, L. and SCREMIN, S.: *Enzyme*, 14, 366-371, 1973.
9. OSTREA, E. M., BASSEL, M., FLEURY, C. A., BARTOS, A. and JESURUN, C. A.: *J. Pediat.*, 102, 426-432, 1983.
10. PIPER, R. F. and HARGREAVES, T.: *Clin. Chim. Acta*, 60, 215-218, 1975.
11. ROBERTSON, A. and BRODERSEN, R.: *J. Pediat.*, 102, 434-438, 1983.
12. SHARP, P., RILEY, C., COOK, G. H. and PINK, P. J. F.: *Clin. Chim. Acta*, 36, 93-98, 1972.

M. E. MUÑOZ, J. GONZÁLEZ and A. ESTELLER

Departamento de Fisiología Animal
Facultad de Farmacia
Salamanca (Spain)

(Received on February 9, 1984)