Stimulation of Insulin Output by Monosaccharides and Monosaccharide Derivatives

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ABSTRACT

POZZA, GUIDO, GIORGIO GALANSINO, HARVEY HOFFELD AND PIERO P. FOÀ. Stimulation of insulin output by monosaccharides and monosaccharide derivatives. Am. J. Physiol. 192(3): 497-500. 1958.—The ability of various sugars and closely related substances to stimulate insulin secretion was studied by means of pancreatic-femoral cross-circulation experiments between hepatectomized donor dogs and normal recipients. In other experiments, the test substance was injected directly into the pancreatic artery of normal dogs. The administration of d-glucose, d-galactose or d-ribose was followed by a prompt hypoglycemia, suggesting insulin secretion; d-arabinose caused an unexplained delayed hypoglycemia, while d-fructose, d-mannose, d-xyllose, l-arabinose, 3-methylglucose, d-glucosamine, galacturonic acid and saline had no effect. The tentative hypothesis that insulin secretion is stimulated by sugars which are both utilizable and insulin-sensitive is offered. No relationship between chemical structure and ability to cause insulin release was found.

HYPERGLYCEMIA obtained by means of oral or parenteral administration of glucose, causes the release of insulin from the pancreas (for references see (1)). This statement is based on numerous experimental observations such as: a) the slow intravenous infusion of glucose is followed by hypoglycemia and increased tolerance for glucose (2, 3); b) the perfusion of an isolated pancreas with glucose solution causes the release of insulin into the perfusate (4); c) pancreatic venous blood from a hyperglycemic donor dog causes hypoglycemia in a recipient dog (5, 6); d) the injection of glucose into the pancreatic artery is followed by a fall in the systemic blood sugar concentration (7-9); e) the administration of glucose causes an apparent increase in plasma insulin activity (10, 11). Recent evidence indicates that, in addition to glucose, prolactin (12), mesoxalate (13) and the hypoglycemic sulfonamides (14, 15) may stimulate insulin release. Sugars other than glucose also may have this property, as suggested by the hypoglycemia frequently observed in galactosemic children (16), especially following galactose administration (17, 18), by the hypoglycemia seen after the injection of d-ribose in man (19) and by the fact that several sugars cause the return of beta granules in pancreatic islets previously suppressed by insulin treatment (20).

The purpose of this work was to investigate if a number of monosaccharides and monosaccharide derivatives can stimulate the release of insulin from the pancreas and if this property is related to their chemical structure.

METHODS

Mongrel dogs of both sexes weighing 10-15 kg were anesthetized with sodium pentobarbital (35 mg/kg, intraperitoneally). Two series of experiments were performed. The first series consisted of six pancreatic-femoral cross-circulation experiments using hepatectomized donor dogs. The donors were prepared as follows: under anesthesia, 1-inch pieces of polyethylene tubing, with a diameter equal to...
about one-third of that of the portal vein and of the inferior vena cava, were ligated tightly to these vessels with double ligatures and then withdrawn, leaving the ligatures in place. In this manner, the vessels were allowed to re-expand to about one-third of their original diameter. Six or more weeks after this preliminary operation, when a well developed collateral circulation could be seen on the abdominal wall, the animals were again anesthetized and portal vein, hepatic artery, common bile duct and inferior vena cava were ligated in the abdomen. In addition the vena cava was ligated above the diaphragm through a small thoracic incision. After this, the lungs were inflated through a tracheal cannula, the chest wound was repaired, the liver removed, the pancreato-duodenal vein cannulated and the experiment carried out as described previously (6). After a 20-minute control period, d-fructose (1 gm/kg) was injected intravenously into the donor dog, and six blood samples were taken from a femoral vein at 10-minute intervals for fructose and glucose determinations. After 1 hour the cross-circulation was interrupted, the donor dog was killed and blood samples were taken from the recipient dog for another hour. This procedure, requiring the simultaneous determination of glucose and of the test substance in the blood of the animals, was found satisfactory when d-fructose was used. However, in the case of other substances, the determination of which is based on copper reduction methods before and after the specific destruction of glucose, the analytical errors were found to be unpredictable and the experimental design was changed. In this second series of experiments, the pancreas was exposed through a mid-line incision and the pancreatic artery was cannulated as close as possible to its origin. Five cubic centimeters of isotonic saline were then injected rapidly to check the placement of the cannula and the adequacy of the collateral blood supply. This was demonstrated by the fact that the pancreas, after having been blanched by the saline, reacquired its normal pink color, within 1 or 2 seconds after the end of the injection.

Following a 30-minute control period, during which three blood samples were collected from an exposed femoral vein, one of the substances under investigation (0.5 gm in 20 cc of saline) was injected into the pancreatic artery by means of a constant infusion pump. The injection lasted exactly 6 minutes and after it, sampling of venous blood was continued for 3 hours. This technique allowed the perfusion of the pancreas with a high concentration of the test substance without injecting it in amounts sufficient to cause a detectable rise in the reducing power of the peripheral blood. Blood glucose was determined according to Nelson (21), fructose according to Roe (22). The statistical significance of the changes in blood glucose concentration was calculated according to Fisher (23).
RESULTS

The results are presented in the form of curves showing average changes in blood sugar concentration. Figure 1 represents the result of cross-circulation experiments in which hepatectomized donor dogs D received d-fructose intravenously. It can be seen that, in the hepatectomized donor, the injected fructose rapidly reaches a constant level, and that the small amounts of it appearing in the circulation of the recipient dog R, are promptly metabolized. At the same time, the glucose concentration in the blood of dog D falls to very low levels as a result of hepatectomy, while the blood sugar of dog R does not vary significantly. Figure 2 shows the results of experiments in which the test substance was injected directly into the pancreatic artery. It may be seen (part A) that no significant changes in blood glucose concentration occur during the pre-injection control period or following the injection of saline, and that a statistically significant ($P < 0.01$) hypoglycemia occurs 45–75 minutes after the injection of d-glucose, or d-galactose into the pancreatic artery. In the case of glucose the maximum decrease in individual experiments, varied between 20 and 35%, while in the case of galactose the maximum decrease varied between 22 and 54%. These maximum effects did not happen at the same time in all experiments resulting in a flattening of the average curve. Part B shows that also the injection of d-ribose is followed by a statistically significant decrease in blood sugar concentration (17–25%, $P < 0.02$) reaching a minimum in 45–75 minutes and that d-arabinose causes a decrease in blood glucose (22–46%, $P < 0.05$), but only 90–180 minutes after the injection. Figure 3 shows that intrapancreatic injections of d-mannose, d-fructose, d-xylose, l-arabinose, 3-methylglucose, d-glucosamine and galacturonic acid, appear to share with glucose the property of stimulating insulin output. This is consistent with the hypothesis that excessive insulin secretion may be responsible for the hypoglycemia of galactosemic infants who, being unable to convert galactose into glucose, could not counteract the effect of this hormone especially after a galactose load. Accordingly, the substitution of ready available sources of glucose for galactose in the diet is followed by rapid improvement in most cases (16–18). Similarly, the ability of d-ribose to stimulate the release of insulin may contribute to the hypoglycemia noted after its intravenous injection in man (24). d-Arabinose injection also is followed by a significant hypoglycemia. This, however, is a delayed phenomenon and, for this reason, does not appear to be the result of a direct effect of the sugar on the pancreas. Thus, of the sugars tried, only d-glucose, d-galactose and d-ribose, causes no significant changes. These results confirm previous observations, cited in (1), and support the belief that this sugar is capable of causing the release of insulin from the pancreas. In addition the results demonstrate that the experimental conditions per se do not cause changes in blood glucose concentration and are adequate for the solution of the problem under investigation. d-Galactose and d-ribose, but not d-fructose, d-mannose, d-xylose, l-arabinose, 3-methylglucose, d-glucosamine and galacturonic acid, appear to share with glucose the property of stimulating insulin output.
seem capable of causing a prompt insulin release, while the delayed effect of d-arabinose cannot be explained satisfactorily at the present time. It is possible that d-arabinose may be converted to glucose by the pancreas itself. A similar conversion into glycogen has been demonstrated in mice (25), but in amounts not as great as that of other sugars, such as d-xylose (25), or d-fructose (26), which were found inactive in these experiments. It is interesting to note that d-glucose, d-galactose and d-ribose, the three sugars found capable of stimulating insulin secretion, are normal body substances tested reveals no relationship between chemical structure and ability to induce insulin release from the pancreas, although only sugars which are both utilisable and insulin-responsible appear to have this property.

REFERENCES