Portal and Peripheral Vein Immunoreactive Insulin Concentrations Following Tolbutamide Administration

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SUMMARY

The effect of tolbutamide on portal and peripheral vein immunoreactive insulin concentrations in man was assessed and compared with that of a glucose stimulus. The portal vein IRI responses to both stimuli were similar. The ratios of peripheral vein to portal vein insulin response (area under the curve) following tolbutamide administration were the same or lower than that following a glucose infusion. DIABETES *20*:168-70, March, 1971.

In a previous report[1] we demonstrated the effect of intravenous glucose on portal and peripheral vein insulin concentrations in nondiabetic subjects. Employing the same technic for obtaining portal plasma as in our previous study (catheterization of the portal vein via the collapsed umbilical vein), we have investigated the effects of tolbutamide on portal and peripheral vein immunoreactive insulin (IRI).

METHODS

Five nondiabetic subjects requiring abdominal exploration were selected to assess the portal and peripheral vein insulin response to tolbutamide. Insulin responses to glucose in ten nondiabetics are included for comparison. For this purpose the results of seven subjects who had appropriately timed blood specimens were taken from our previously published data[1] and combined with the results of three additional nondiabetics receiving the glucose stimulus. The patients had a variety of conditions requiring surgery, which are listed in table 1 along with information concerning age, sex, race, and determinants of glucose tolerance. Liver function tests were normal in all subjects except patient E. G. who had obstructive jaundice due to choledocholithiasis.

After an overnight fast, the patients were taken to the operating room and prepared in the usual fashion for an abdominal exploration. No general anesthetic was given although some of the patients received 5 mg. Valium or 50 mg. Demerol prior to the procedure. A catheter for withdrawal of blood samples was placed in an antecubital vein prior to the operative procedure and the catheter was kept patent by a saline infusion delivered at a slow rate. Under local anesthesia with 1 per cent lidocaine, the umbilical vein was exposed through an extraperitoneal upper abdominal midline incision and cannulated with a size 9 ureteral catheter. The catheter was then passed into the left branch of the portal vein just past its entrance into the liver.

After two baseline blood samples one minute apart had been obtained simultaneously from the portal and antecubital veins, either 1 gm. tolbutamide or 25 gm. glucose was infused at a constant rate over two minutes in the opposite antecubital vein. Heparinized blood samples from the portal and antecubital veins were then obtained simultaneously during the infusion at 60, 90, and 120 seconds after start of the infusion and at ½, 1, 3, 5, 8, 10, and 15 minutes after completion of the tolbutamide or glucose infusion. Plasma IRI was determined by a double antibody radioimmunoassay method[2] utilizing insulin I-125 as tracer.

RESULTS AND DISCUSSION

Figure 1 shows the portal vein IRI concentrations during and following a two-minute tolbutamide infusion in five nondiabetic subjects. One of the five subjects had such an excessive insulin response that it is shown separately. As he was the only overweight patient (> 40 per cent above ideal weight) in the group, obesity may have accounted for his unusually high insulin concentrations. For comparison, the portal vein

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TABLE 1

Subjects for portal vein catheterization

Patient	Age	Sex	Race	FBS (mg. per 100 ml.)	Oral GTT	Diagnosis
			Nondiabetics receiving intravenous glucose			
H.H.	65	M	Negro	73		Negative exploration
H.P.	30	M	Caucasian	83	Normal	Duodenal ulcer
T.D.	35	M	Negro	83	Normal	Abdominal tuberculosis
E.G.	52	M	Caucasian	80		Cholelithiasis and choledocholithiasis
E.J.	44	M	Negro	88	Normal	Adenocarcinoma rectum
G.M.	71	M	Negro	88	Normal	Negative exploration
L.J.	74	M	Negro	93	Normal	Congenital duodenal webs
E.F.	58	M	Negro	76	Normal	Gastric ulcer
J.H.	39	M	Caucasian	82	Normal	Cholelithiasis
A.S.	74	F	Negro	92	Normal	Adenocarcinoma rectum
			Nondiabetics receiving intravenous tolbutamide			
J.W.	27	M	Caucasian	88	Normal	Duodenal ulcer
B.A.	44	M	Negro	77	Normal	Gastric ulcer
F.F.	28	M	Negro	80		Duodenal ulcer
C.M.	47	M	Negro	76	Normal	Cholecystitis
C.J.	62	M	Negro	90		Duodenal ulcer

insulin response to 25 gm. glucose given intravenously to ten nondiabetics is included. The responses to glucose and tolbutamide were similar. The peak IRI response to tolbutamide occurred thirty to sixty seconds earlier than that to glucose but this may be a manifestation of the threshold stimulus having been reached earlier with tolbutamide. Peak insulin concentrations in every case occurred during the two minutes that the stimulus was being administered.

Portal vein IRI concentrations at five to fifteen

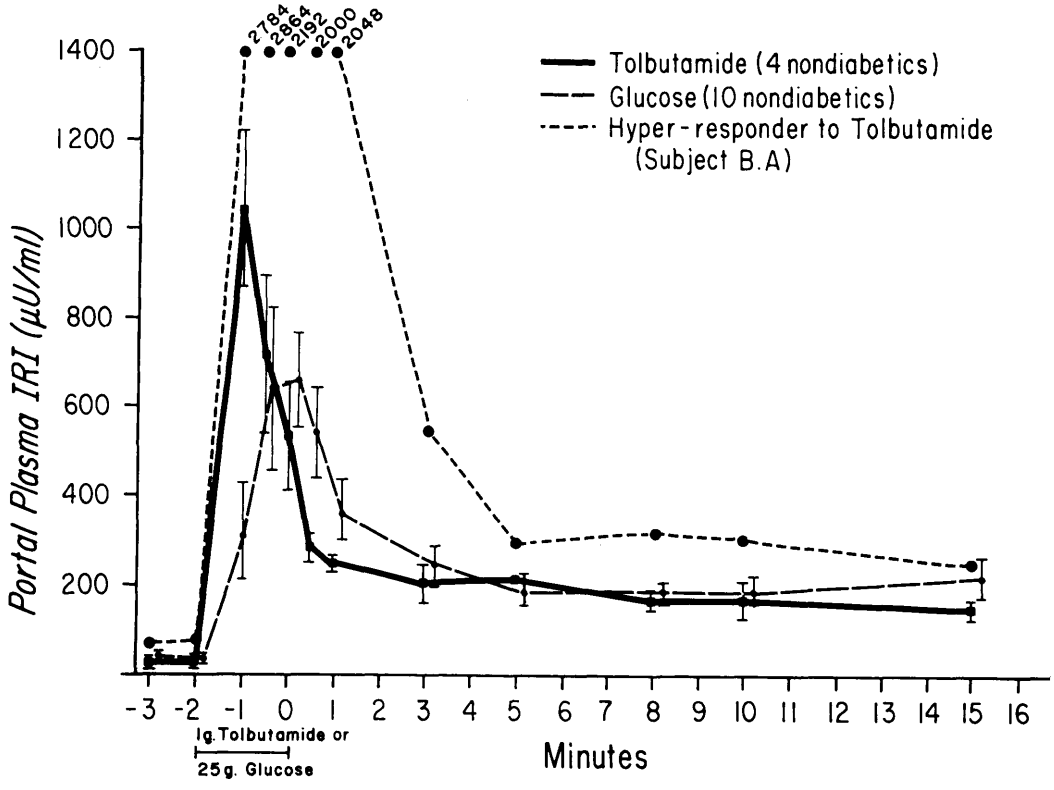

FIG. 1. Portal vein IRI during and following a two-minute infusion of either tolbutamide (1 gm.) or glucose (25 gm.) in nondiabetic subjects. Means ± S.E.M. are shown.

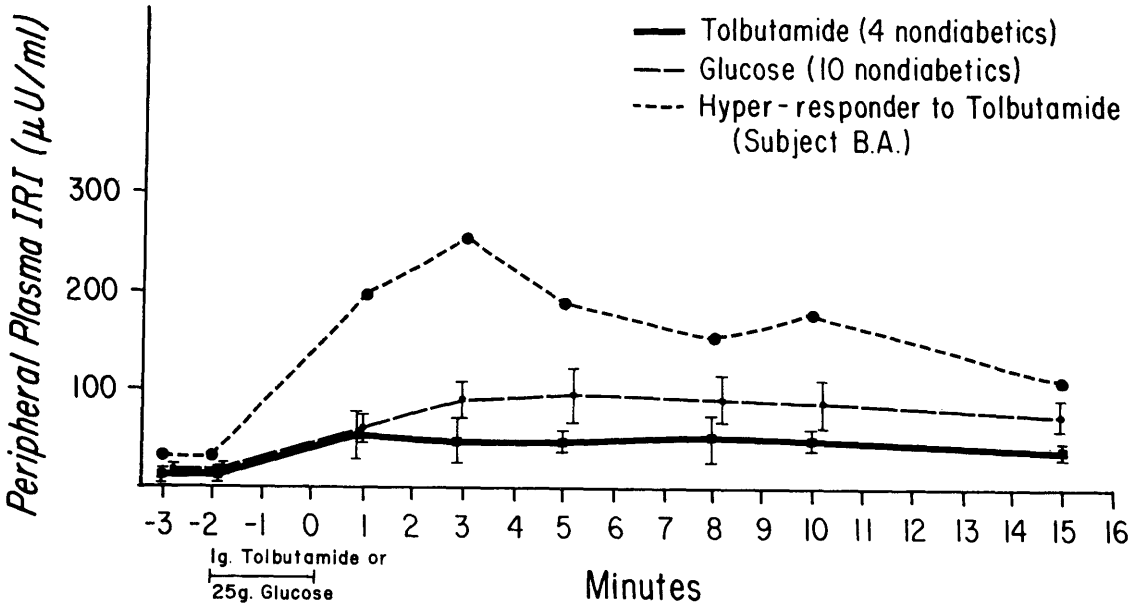

FIG. 2. Peripheral vein IRI following a two-minute infusion of either tolbutamide (1 gm.) or glucose (25 gm.) in nondiabetic subjects. Means ± S.E.M. are shown.

minutes (late insulin response) following tolbutamide administration were surprisingly well maintained at a level comparable to those following glucose administration. Studies with the isolated perfused rat pancreas by Curry, Bennett, and Grodsky have indicated that the late insulin response to tolbutamide is greatly impoverished compared with that to glucose.[3] Perhaps this discrepancy might be explained by the recirculation of tolbutamide which occurs in a closed system such as in our subjects, but not in an open perfusion system.

Peripheral vein IRI concentrations following tolbutamide and glucose administration are shown in figure 2. Again, the values of the hyper-responder to tolbutamide are shown separately. Although there is no statistically significant difference at any time interval, the peripheral insulin concentrations were somewhat lower following tolbutamide (excluding the hyper-responder) than after glucose administration. This is also reflected in the ratios of the peripheral vein to portal vein insulin response after each stimulus. Insulin response curves for both the peripheral and portal vein were constructed for each stimulus and the areas under the curves were integrated. The peripheral vein to portal vein IRI response (area under the curve) ratios were .27 ± .04 and .17 ± .04 to the glucose and tolbutamide stimuli, respectively. Although the peripheral to portal vein insulin response ratio was higher after glucose, the difference is not statistically significant ($.1 > p > .05$).

The equal or lower ratios (peripheral to portal vein IRI response) after tolbutamide do not support the notion that tolbutamide decreases hepatic uptake of insulin. Marshall, Gingerich, and Wright have demonstrated decreased uptake of insulin by the perfused rat liver under the influence of tolbutamide.[4] A theory compatible with both the findings of the later investigators and the somewhat lower than anticipated peripheral insulin concentrations in our subjects following tolbutamide administration is the possibility that tolbutamide might increase peripheral uptake of insulin. In vitro studies by Feldman and Lebovitz,[5] showing a normal rate of disappearance of media insulin incubated in the presence of tolbutamide and rat diaphragms, do not exclude other tissue sites for potential tolbutamide enhanced tissue uptake of insulin.

REFERENCES

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