Uniphasic Insulin-secretory Response in the Pancreatic Vein of Dogs After an Enteric Glucose Load

Antonio R. Chacra, M.D., Yoshikuni Fujita, M.D., Arthur L. Herron, Jr., B.S., and Holbrooke S. Seltzer, M.D., Dallas

SUMMARY

The insulin secretory response to an enteric glucose load was measured in 11 dogs after intrajejunal instillation of a 25 per cent glucose solution (1.75 gm./kg.) in five minutes. Insulin outflow rate was measured every minute for 10 minutes, then at increasing intervals through 60 minutes. Starting at two minutes after onset of glucose loading, mean arterial plasma glucose rose steadily throughout the hour. This was paralleled by a similarly progressive rise in mean pancreatic venous plasma insulin output starting at seven minutes and peaking at 50 minutes, despite partial masking by a simultaneous fall in pancreatic venous plasma flow rate after the fourth minute. The data indicate that the normal insulin response to an enterically administered glucose stimulus is a smoothly rising uniphasic one, in contrast to the typical biphasic insulin response to a "square-wave" intravenous glucose stimulus. DIABETES *27*:21-26, January, 1978.

INTRODUCTION

In 1968 Curry, Bennett, and Grodsky[1] first described the now familiar "biphasic insulin response" to a unique, nonphysiologic glucose stimulus. As shown in figure 1, when they perfused an isolated rat pancreas with a "square-wave" glucose stimulus of 300 mg. per 100 ml. from 0 minutes to 40 minutes, they demonstrated a sudden spike of insulin secretion into the pancreatic vein at three minutes, followed by a sharp fall to a nadir at five minutes and then a slowly progressive increase in insulin output during the rest of the infusion. The ready repeatability of this biphasic insulin response to a sustained hyperglycemic stimulus by Curry and his associates[2,3] and by many other workers[4-6] led to the hypothesis of "two compartments"* of insulin release from the islets—one a small compartment of preformed, stored insulin for immediate release upon glycemic demand and another larger, slowly activated compartment of insulin synthesis in response to sustained hyperglycemia.[2] Subsequently, when Porte and his co-workers demonstrated transient spikes of plasma insulin levels in normal subjects after short bursts of intravenous glucose stimulus superimposed on sustained glucose infusion but no such insulin spike in mild diabetics after similar glucose challenge, they also postulated that there were "two pools" of insulin secretion,[7,8] and that the earliest clinical stage of diabetes might be characterized by impaired responsiveness of the small pool of stored insulin, without a change in the larger pool of insulin synthesis.[9] Finally, as the idea of the "biphasic insulin response to glucose stimulus" became more ingrained in investigators' minds, and as the special conditions under which it was first demonstrated were forgotten, one began to see references to the "typical biphasic response" after acute, two-to-five minute infusions of intravenous glucose[10-12] and, by implication, even after oral or other enteric glucose loads.[13-15] For example, when Albisser and his associates[14] were developing their artificial pancreas for minute-to-minute control of blood sugar levels, they attributed the need for a bolus of intravenous insulin shortly after administering an oral glucose load to the need for mimicking the biphasic insulin response rather than to the actual need of overcoming the 4½-minute time lag between rising plasma glucose

From the Departments of Internal Medicine, Veterans Administration Hospital and the University of Texas Southwestern Medical School, Dallas, Texas.

Address reprint requests to Holbrooke S. Seltzer, M.D., Veterans Administration Hospital, 4500 S. Lancaster Road, Dallas, Texas 75216.

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*See DISCUSSION for Curry's dissenting view of the two-compartment thesis.

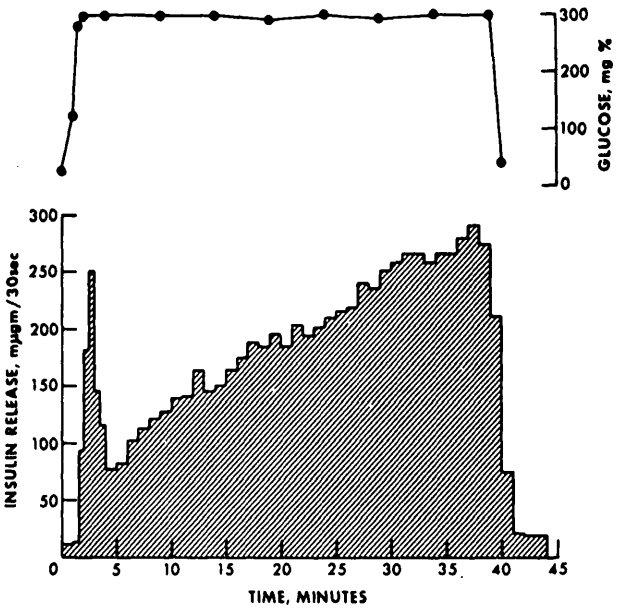

FIG. 1. Demonstration by Curry et al. of the biphasic insulin response of perfused rat pancreas to a "square-wave" glucose stimulus of 300 mg. per 100 ml. for 40 minutes.[1]

levels and subsequent insulin response by the electronic device.

From the outset, however, the present authors have regarded the biphasic insulin response not as a physiologic phenomenon but, instead, as a pharmacologic one that is basically irrelevant to the normal insulin response to an oral glucose load. Rather than representing an intrinsic property of normal islets, we considered the biphasic response to a square-wave stimulus to reflect the previous degree of beta cell activity. In that regard, we recently demonstrated in dogs[16] that the insulin response to a square-wave glucose stimulus depends on antecedent carbohydrate intake, with essentially a square-wave insulin response paralleling a square-wave glucose stimulus in dogs on high carbohydrate intake, in contrast to essentially no insulin response in chronically starved animals.

The present report demonstrates that instillation of an intrajejunal (i.e., "oral") glucose load in dogs is followed by a slowly progressive, parallel rise in both arterial glucose levels and insulin secretion into the pancreaticoduodenal vein.

METHODS AND MATERIALS

Eleven male mongrel dogs were used, all weighing between 21 and 31 kg. Animals received an ordinary laboratory diet consisting of 8 oz. of Vigo dog food and 8 oz. of Purina dog chow daily. This was the same diet that preceded the typical biphasic insulin response to a square-wave 300 mg. per 100 ml. glucose stimulus demonstrated previously.[16] After an overnight fast, dogs were anesthetized with Nembutal (22 mg./kg.) and laparotomized by a midline incision. The free portion of the duodenum was delivered into the wound, and a T-tube was inserted in the cranial pancreaticoduodenal vein about 2 to 3 cm. from its confluence with the portal vein. A length of plastic tubing containing a 1.0-ml. volume connected the T-tube to a three-way stopcock. Intermittent occlu-

TABLE 1

Pancreatic venous plasma insulin output after intrajejunal glucose load (1.75 gm./kg.) in 11 dogs

	Minutes										
	−10	−5	0	Baseline*	1	2	3	4	5	6	7
	Femoral arterial plasma glucose (mg./100 ml.)										
Mean	115	115	116	115	115	116	117	118	120	122	128
S.E.M.	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 5	± 4
"P"†											< .05
	Pancreatic venous plasma outflow rate (ml./min.)										
Mean	7.0	7.0	7.0	7.0	6.8	6.9	6.9	6.9	6.4	6.3	5.9
S.E.M.	±0.3	±0.4	±0.4	±0.4	±0.4	±0.5	±0.5	±0.6	±0.5	±0.5	±0.4
"P"											< 0.05
	Pancreatic venous plasma insulin concentration (μU./ml.)										
Mean	644	647	601	630	678	632	611	666	679	708	855
S.E.M.	±60	±66	±46	±56	±98	±67	±61	±99	±136	±105	±131
"P"											
	Pancreatic venous plasma insulin output (μU./min.)										
Mean	4,480	4,513	4,178	4,391	4,450	4,152	4,009	4,332	4,067	4,146	4,694
S.E.M.	±408	±444	±435	±398	±678	±445	±444	±567	±650	±426	±515
"P"											

*Mean of the three pre-glucose values.
†Significance of difference from mean baseline value.

sion of the proximal pancreatic vein with an umbilical-tape choker enabled diversion of pancreatic venous outflow through the plastic tubing into collecting tubes. At sampling times the proximal pancreatic vein was occluded, and the number of seconds required to collect exactly 10.0 ml. of pancreatic venous blood was timed by stop watch and converted to milliliters per minute outflow rate of pancreatic venous whole blood. The "plasmacrit" (100 per cent—hematocrit per cent) was determined on all whole-blood samples by a routine micromethod, and the outflow rate of pancreatic venous plasma was determined by the formula:

Whole-blood outflow rate (ml./min.) × plasmacrit (%) = plasma outflow rate (ml./min.).

A 16-gauge plastic tube was inserted within the jejunum via a small incision about 5 cm. below the distal tip of the right pancreatic limb on the duodenum. A femoral vein and a femoral artery were cannulated with Cournand needles. After the T-tube, the intrajejunal tube, and both needles were inserted, a slow intravenous drip of physiologic saline was started, and the dog was given 1,000 USP units of heparin per 10 kg. of body weight intravenously and was allowed to stabilize for 60 minutes before baseline samples were collected.

Following stabilization, simultaneous baseline blood samples were obtained from the pancreaticoduodenal vein and a femoral artery at −10, −5, and 0 min. At zero time a 25 per cent solution of glucose was instilled intrajejunally over a five-minute period, the glucose load being 1.75 gm. per kilogram. Pancreatic venous and femoral arterial samples were drawn every minute for the first 10 minutes, then at 15, 20, 25, 30, 40, 50, and 60 min. During procurement of these blood samples, the infusion rate of intravenous saline was increased to replace entirely the volume of blood withdrawn. On all pancreatic venous samples, plasma insulin concentration was determined by a modification of the Yalow-Berson radioimmunoassay[17] that uses dextran-coated charcoal instead of immunoelectrophoresis for separation of free from bound ^{125}I-labeled insulin.[18] Plasma insulin outflow rates were calculated from the formula:

Plasma insulin concentration (μU./ml.) × plasma outflow rate (ml./min.) = plasma insulin outflow rate (μU./min.).

Femoral arterial blood samples were spun down immediately, and plasma glucose concentrations were determined on a Beckman Glucose Analyzer.[19]

RESULTS

Femoral arterial plasma glucose concentrations (table 1, figure 2). For all samples, the mean of the −10-, −5-, and 0-minute values was used as the baseline value. The mean (± S.E.M.) baseline femoral arterial plasma glucose level of 115 ± 5 mg. per 100 ml. remained unchanged for one minute, then rose slowly and progressively to a maximal value of 244 ± 18 mg. per 100

TABLE 1 (cont.)
Pancreatic venous plasma insulin output after intrajejunal glucose load (1.75 gm./kg.) in 11 dogs

	Minutes									
	8	9	10	15	20	25	30	40	50	60
	Femoral arterial plasma glucose (mg./100 ml.)									
Mean	133	137	147	176	194	211	221	236	241	244
S.E.M.	± 4	± 5	± 6	± 9	±11	±13	±13	±13	±15	±18
"P"	<0.01	<0.01	<0.005	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Pancreatic venous plasma outflow rate (ml./min.)									
Mean	5.4	5.7	5.6	5.6	5.5	6.0	6.3	6.3	6.4	6.4
S.E.M.	±0.5	±0.4	±0.4	±0.3	±0.4	±0.5	±0.5	±0.4	±0.3	±0.3
"P"	<0.02	<0.025	<0.02	<0.005	<0.025					
	Pancreatic venous plasma insulin concentration (μU./ml.)									
Mean	911	936	999	1,205	1,961	1,936	1,988	2,111	2,246	2,187
S.E.M.	±125	±134	±155	±139	±280	±214	±244	±242	±240	±261
"P"		<0.05	<0.05	<0.005	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Pancreatic venous plasma insulin output (μU./min.)									
Mean	4,451	5,121	5,366	6,585	10,572	11,479	12,032	12,909	13,848	13,127
S.E.M.	±402	±586	±716	±825	±1,190	±1,304	±1,145	±1,328	±1,038	±1,195
"P"				<0.05	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

*Mean of the three pre-glucose values.
†Significance of difference from mean baseline value.

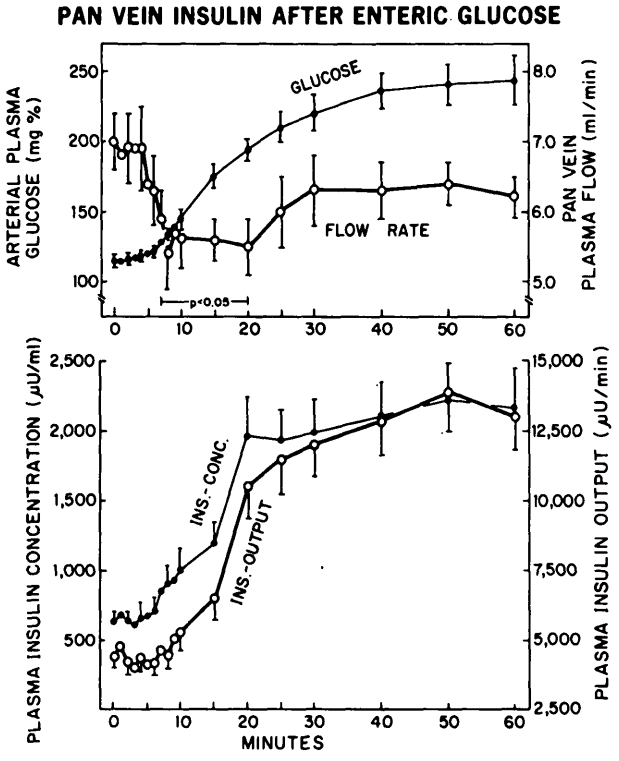

FIG. 2. After intrajejunal instillation of glucose (1.75 gm. per kilogram from 0-5 minutes), progressively rising arterial plasma glucose levels elicited essentially parallel increases in both pancreatic venous plasma insulin concentrations (μU./ml.) and secretory rates (μU./min.). The slightly slower rise of insulin output was due to a significant fall in pancreatic venous plasma flow rates between seven and 20 minutes ($p < 0.05$ or greater).

ml. at 60 minutes. The plasma glucose level was significantly higher than baseline ($p < 0.05$ or greater) at seven minutes and thereafter.

Pancreatic venous plasma outflow rates (table 1, figure 2). In all 11 animals the pancreatic venous plasma outflow rate decreased significantly below baseline after instillation of glucose was begun, with the mean baseline rate of 7.0 ± 0.4 ml. per minute falling to 5.9 ± 0.4 ml. per minute at seven minutes ($p < 0.05$) and remaining clearly below the starting level through 20 minutes ($p < 0.025$ or greater). In nine of the 11 dogs the plasma outflow rate was still below baseline at 60 minutes.

Pancreatic venous plasma insulin concentrations (table 1, figure 2). The mean pancreaticoduodenal venous plasma insulin concentration at baseline was 630 ± 56 μU. per milliliter; this value fell slightly to a nadir of 611 ± 61 μU. per milliliter (N.S.) at three minutes after starting the intrajejunal instillation of glucose, then rose progressively to a maximum value of 2,246 ± 240 μU. per milliliter at 50 minutes. Pancreatic venous insulin concentrations were significantly greater than baseline ($p < 0.05$ or better) at nine minutes and thereafter.

Pancreatic venous plasma insulin outflow rates (table 1, figure 2). The mean pancreatic venous plasma insulin outflow rate at baseline was 4,391 ± 398 μU. per minute. This value fell slightly to a level of 4,009 ± 444 μU. per minute at three minutes (N.S.) and remained below baseline rate through six minutes. Pancreatic venous insulin output then rose progressively to a maximum output of 13,848 ± 1,038 μU. per minute at 50 minutes, and it was significantly higher than the baseline rate ($p < 0.05$ or greater) at 15 minutes after the start of intrajejunal glucose instillation and thereafter.

DISCUSSION

The present data show that when glucose is administered essentially physiologically, i.e., by the gastrointestinal route, the resulting gradual rise of arterial glucose levels is accompanied by an appropriately parallel rise in pancreatic insulin secretion. In other words, following an enteric glucose load, there is no "biphasic response" because normally responsive islets are geared to respond proportionately to rising glucose levels until sufficient insulin secretion disposes of circulating glucose intrahepatically or peripherally, whereupon both glucose and insulin levels fall toward baseline together. On the other hand, as was previously demonstrated by the authors,[16] the biphasic insulin response to a square-wave glucose stimulus is a pharmacologic response to a similarly pharmacologic stimulus, and it is characterized by immediate release of preformed insulin followed by a sharp fall in hormonal output until the synthesis of new insulin can catch up with sustained hyperglycemic demand. At the same time, this artificial response can itself be manipulated by altering the antecedent glucose intake, which conditions the speed and magnitude of beta cell responsiveness.[16] The importance of emphasizing that the normal insulin response to an ordinary oral (enteric) glucose load is a slow uniphasic rise of insulin secretion is to clarify thinking about physiologic insulin responsiveness and to establish the fact that there are not "two pools" of fast-versus-slow insulin secretion[2,7-9] but, rather, one continuous pool of synthesis, storage, and release.

In this regard, several years ago Curry himself clearly recognized and demonstrated the greatly different insulin secretory response to a slowly rising glucose stimulus as compared with a square-wave

one.[3] Perfusion of his rat pancreas preparation at gradually rising glucose concentration (from 30 to 300 mg./100 ml. in 80 minutes) was accompanied by parallel stepwise enhancement of insulin output (from 3.4 to 155 ng./30 sec. in 80 minutes). He also found that a square-wave glucose stimulus (300 mg./100 ml.) imposed five minutes after stopping the slow-rise infusion elicited a faster (onset within 1.5 minutes) and higher (476 ng./30 sec.) peak insulin response during the first phase than when the same square-wave stimulus was given without prior glucose stimulation (onset of rise 2.5 minutes after start of stimulus, peak value of first phase 110 ng./30 sec.). This finding demonstrated experimentally what clinicians know empirically; namely, that a high-carbohydrate dietary preparation increases beta-cell responsiveness to a given glucose challenge.[16] Finally, Curry pointed out that the latter enhancement of insulin response to a square-wave glucose stimulus by a prior slow-rise glucose stimulus—rather than a depressed response that would reflect previous depletion of stored insulin—militated against the two-compartment model for insulin storage and release originally proposed by his associates[2] but to which Curry himself never subscribed.[20]

The observation that the type of insulin response depends on the rate of glucose stimulus was subsequently embellished by Grodsky, who postulated an all-embracing "threshold distribution hypothesis" in which "packets" of stored insulin are released at progressively higher levels of glucose stimulation.[21,22] He found that, although immediate spikes of plasma insulin release from the perfused rat pancreas could be induced either by successive "staircase" increments of plasma glucose of 50 mg. per 100 ml. or by increasing the plasma glucose level rapidly at a constant rate (from 0 to 250 mg. per 100 ml. in five minutes), when the plasma glucose level was steadily increased at a slow rate (from 50 to 250 mg. per 100 ml. in 60 minutes) there was no early peak response but, instead, a gradually rising insulin curve throughout the hour of infusion. In discussing these different effects of fast-versus-gradual stimulation of insulin release, Grodsky says, ". . . the slow rise of glucose which occurs postprandially should not produce detectable phases of insulin secretion."[22] Thus, he too demonstrated in the isolated, perfused rat pancreas that beta-cell responsiveness to intravenous glucose is not in fact a fixed response but, rather, a variable one depending on qualitative modifications in glucose stimulation.

On the other hand, lack of awareness of the foregoing interpretations of the biphasic insulin response to square-wave glucose stimulus has led to misreading of the insulin response to oral or other enteric glucose loads. The discussion by Albisser et al.[14] of the need for a bolus of intravenous insulin to prevent hyperglycemia after an oral glucose load has already been cited in the INTRODUCTION. In addition, when Kaden and co-workers[15] estimated the total amount of insulin reaching the liver via the portal vein and hepatic artery after intraduodenal administration of 50 per cent glucose to dogs, they found "two peaks of insulin secretion" in 10 of 14 dogs. However, the initial "peaks" were in fact transient maximal values that occurred between nine and 40 minutes in nine dogs, but which in no way resembled the typical biphasic insulin response illustrated in figure 1.

In the present study, intrajejunal instillation of the glucose load was used instead of intragastric administration in order to circumvent the delayed gastric emptying that occurs in the anesthetized supine animal. The prompt rise in arterial glucose levels before the end of the five-minute instillation period simulated the physiologic rate of absorption and gradual rise in both inferior vena caval glucose and pancreatic venous insulin concentrations found by Unger's group in previously cannulated, awake, standing dogs after ingestion by gavage of an "oral" glucose load.[23] Thus, although intrajejunal instillation of glucose in the anesthetized, laparotomized animal is not strictly physiologic, it is as close to that state as possible when the objective is to measure actual insulin output directly, and the patterns of glycemic stimulus and insulin response appear to be the same.

The present data also illustrate the need to measure pancreatic venous insulin output specifically, rather than simply determining plasma insulin concentrations, when assessing the insulin response to a glycemic stimulus. In contrast to our previous study, during which pancreatic venous insulin output was measured in response to a square-wave *intravenous* glucose stimulus[16] and which actually showed a significant rise in pancreatic venous plasma flow from 9.6 ± 0.6 ml./min. to a peak of 14.8 ± 0.8 ml. in five minutes ($p < 0.001$), in the present study the absorption of an *enterically* administered glucose load significantly decreased the rate of pancreatic venous plasma flow and to some extent falsely elevated the concomitant insulin concentrations. This was evidenced by the fact that, although pancreatic venous plasma insulin concentrations were significantly higher than baseline values at nine minutes and thereafter, total pancreatic venous insulin output was not

significantly higher than baseline until 15 minutes and thereafter (table 1). Although decreased regional intestinal blood flow after an enteric glucose load is surprising at first glance, since enterically administered nutrients uniformly cause increased flow through the organs and the splanchnic area perfused by the superior mesenteric artery,[24-26] other published data confirm and explain the finding. Kaden and his co-workers[15] measured portal venous blood flow and portal venous plasma insulin concentrations in acutely laparotomized dogs after intraduodenal administration of 50 gm. of 50 per cent glucose. They found no increase in portal venous blood flow and, in fact, noted a slight but insignificant decline from nine minutes to 120 minutes after giving glucose. Subsequently, Chou et al.[24] pointed out that increased intestinal blood flow may be confined to the gut segment exposed to hypertonic glucose.[27,28] Since the intrajejunal glucose load in the present study was instilled more than 5 cm. below the distal tip of the right pancreatic limb on the duodenal wall, the effects of glucose absorption on local blood flow probably took place well below the area drained by the cranial pancreaticoduodenal vein, from which our blood flow and plasma insulin samples were obtained.

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