Glucose Uptake and Production During the Oral Glucose Tolerance Test

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SUMMARY

During the three hours required for absorption of most of a U-C-14-glucose load (1 gm./kg.) given orally to an intact unanesthetized dog in the postabsorptive state, about three quarters of the load reaches the peripheral circulation. The absence of randomization of the label, seen when an equal oral load of 6-C-14-glucose is given, indicates that the glucose reaching the peripheral circulation has not been fragmented, then resynthesized into glucose. During the three-hour period, only 0.34 gm. per kilogram of new (unlabeled) glucose is released by liver instead of the 0.63 gm. per kilogram which would have been produced in the absence of oral glucose; the uptake of the glucose of peripheral circulating blood is 1.03 gm. per kilogram instead of 0.63 gm. per kilogram. Endogenous insulin secreted in response to the oral load exerts a somewhat larger effect to decrease hepatic glucose release (relative to the increase in glucose uptake from peripheral blood) than is the case when insulin is given by peripheral vein. DIABETES *17*:415-21, July, 1968.

The glucose tolerance test, in which a glucose load is administered orally or intravenously, continues to serve as a useful indicator of abnormalities in glucose metabolism. The changes in blood glucose concentration which form the basis for the interpretation of the test are influenced by several factors besides the rate of uptake of the glucose load by the tissues.

The "K value" for the intravenous test, which appears to represent the velocity constant of a first order disappearance process in which glucose concentration determines the rate of glucose uptake by the tissues, is most likely a hybrid number. The early fall in blood glucose concentration after intravenous glucose injection is hastened by the spreading of the injected load throughout the glucose space. This is evidenced by the mixing of injected C-14-glucose with the body glucose. This mixing process has a slow component and so becomes of negligible importance only after about forty-five minutes, at least in the dog.[1] While the above influence is losing its force, the influence of decreased glucose release by the liver is taking its place in hastening the fall of the blood glucose concentration. This decrease in glucose release develops gradually[2] so that glucose release cannot reasonably be considered either zero or constant during the fall in blood glucose concentration by which a "K value" is measured.

The oral glucose tolerance test mimics more closely the situation met with in daily life. Moreover, it has been reported recently that the oral administration of glucose evokes the secretion of intestinal factors which secondarily stimulate insulin secretion above the level seen when glucose is given intravenously.[3,4] It is conceivable that this greater amount of insulin, entering by way of the portal vein and so reaching the liver first, might shut off glucose release promptly and completely. This might eliminate one of the variable factors which adds to the influence of increased glucose uptake in causing the fall of glucose concentration which is seen in the intravenous glucose tolerance test.

For these reasons experiments were undertaken to measure in normal dogs the effect of an oral glucose load on endogenous glucose production and on glucose uptake from the blood by the tissues, along with measurements of plasma insulin concentration by immunoassay. Simultaneous observations of the rate at which the administered glucose reached the circulation were made feasible by using U-C-14-glucose as the oral load and 6-C-14-glucose to measure total glucose input (including endogenous glucose release) into the circulation.

METHODS

Trained dogs were kept on a standard diet which has been described.[2] A priming dose (30 μc) followed

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by a continuous infusion (30 μc/125 min.) of a trace amount (in saline) of 6-C-14-glucose was administered to the eighteen-hour fasted dog by peripheral vein[2] for a three-hour period prior to stomach tube administration of a bulk amount of an aqueous solution of U-C-14-glucose (1 gm. glucose kg. body weight; about 50 μc total C-14; a total volume of about 100 ml.). Blood samples were collected (heparin) by way of an indwelling polyethylene catheter in the jugular vein, plasma was collected after centrifugation; the samples were taken at intervals prior to the oral glucose load, and for at least 180 minutes after administration of the load. The samples were analyzed for glucose content,[2] and for C-14 in the whole molecule (glucosotriazole derivative)[2] and in carbon 6 only (dimedon derivative after periodate oxidation)[5] by methods previously described. In one control experiment an unlabeled glucose load of the same size was given in the same way during intravenous 6-C-14-glucose infusion in trace amount; in another control experiment no intravenous C-14-glucose was given, and the bulk oral glucose load contained 6-C-14-glucose. Plasma insulin concentrations were measured by radioimmunoassay by a modification of the Yalow and Berson[6] technic.

Correction for recycling of C-14 as determined during infusion of 6-C-14-glucose alone

The C-14 activity in the dimedon derivative (carbon 6) of plasma glucose was expressed as μc per gm. glucose carbon (includes weights of all carbon atoms, 1 through 6). Let this value be D. This value was less than the total C-14 content of the whole glucose molecule (also in μc/gm. glucose carbon) as determined by the C-14 activity in the glucosotriazole derivative (carbons 1 through 6). Let the difference be E; this was the C-14 in carbons 1 through 5, which was due to resynthesis of glucose from three carbon fragments derived from plasma glucose taken up by the tissues. As is customarily done,[7] the assumption was made that the resynthesis of glucose puts an equal amount of C-14 back into carbons 1, 2, 5 and 6. Then D—1/3 E was the specific activity of the plasma glucose (in μc/gm. total glucose carbon) corrected for recycling of C-14.

Separate contributions of 6-C-14-glucose and U-C-14-glucose to plasma glucose specific activity

The value of E was observed to increase moderately between sixty minutes and 180 minutes of 6-C-14-glucose infusion; it remained unchanged from its 120 to 180-minute value over the 180 to 360-minute period in an experiment in which an unlabeled oral glucose load was given (table 3). Consequently, the mean value of E observed in the 120 to 180-minute period of 6-C-14 glucose infusion (just prior to the U-C-14-glucose load) was used to remove the influence of the recycled C-14 from the counting data obtained during the absorption of the glucose load. The C-14 activity in the dimedon derivative (expressed as μc/gm. total glucose carbon) had 1/3 E subtracted from it; let the corrected value be G. The C-14 activity in the glucosotriazole derivative (expressed as μc/gm. total glucose carbon) had 4/3 E subtracted from it; let the corrected value be H. Then H—G represented the activity in carbons 1 through 5 due to U-C-14 glucose; the total activity due to U-C-14-glucose in all carbons of plasma glucose was then 6/5(H—G) in μc per gm. total glucose carbon. The activity in carbon 6 (dimedon derivative) denoted as G, included contributions from U-C-14-glucose as well as from 6-C-14-glucose. The value G-1/5(H—G) was then the activity in plasma glucose due to 6-C-14-glucose, in μc per gm. total glucose carbon.

Calculation of the rate of inflow of the oral glucose load, and of the endogenous glucose production rate

The glucose space was calculated from the corrected plasma glucose specific activities (D—1/3 E) observed during 6-C-14-glucose infusion prior to administration of the oral glucose load; the calculation is described elsewhere.[2] Using this value to calculate B_t, the glucose half-pool size, at any given plasma glucose concentration, the equations described elsewhere[8] were used to calculate glucose input and outflow rates between successive observed values of plasma glucose concentration and specific activity during the absorption of the oral glucose load. Specific activities due to 6-C-14-glucose were used in equations (4a) and (5a) of the previous publication,[8] along with the known infusion rate (F μc C-14/min.) of 6-C-14-glucose, to calculate total input and outflow of glucose. This included both endogenous and oral load glucose inputs to the circulating blood. Equation (4a) was then used a second time, inserting this time the specific activities due to U-C-14-glucose and the value for the total glucose input obtained by the first use of equation (4a). This allowed calculation between successive observation points of F′ (μc C-14/min.), the rate of input of C-14 due to absorption of the oral U-C-14-glucose load. Having found F′ for the interval, the oral load glucose input (in gm. C/min.) could be calculated, since the μc per gm. C in the glucose load was known. This value subtracted from total glucose input gave the endogenous glucose production rate, in gm. C/min.

RESULTS

Figure 1 shows plasma glucose concentration, glucose release by liver, glucose transfer from gut to peripheral blood, and glucose uptake from blood as judged by observations on samples of peripheral blood in a typical oral glucose load experiment. The calculated values of plasma glucose specific activity due to 6-C-14-glucose and due to U-C-14-glucose are given also.

Table 1 gives the results of the four experiments in which load absorption and endogenous glucose release were measured simultaneously. The prompt increase in plasma insulin concentration when glucose is absorbed is evident; also the prompt reversion of plasma insulin concentration to control levels when glucose load absorption tapers off. Enhanced glucose uptake by the tissues continues after the fall in plasma insulin concentration has occurred; this is in accord with findings in experiments done previously, in which the intravenous infusion of insulin was stopped abruptly. However in these previous experiments the depression of unlabeled glucose release was terminated abruptly when insulin infusion was stopped, whereas in the present circumstances the depression of unlabeled glucose release continues for one-half hour to one hour after plasma insulin concentration has reverted to normal. It is quite possible that continued extra insulin secretion, in amount insufficient to maintain an elevated peripheral blood insulin concentration, is responsible for the continued depression of unlabeled glucose release by the liver.

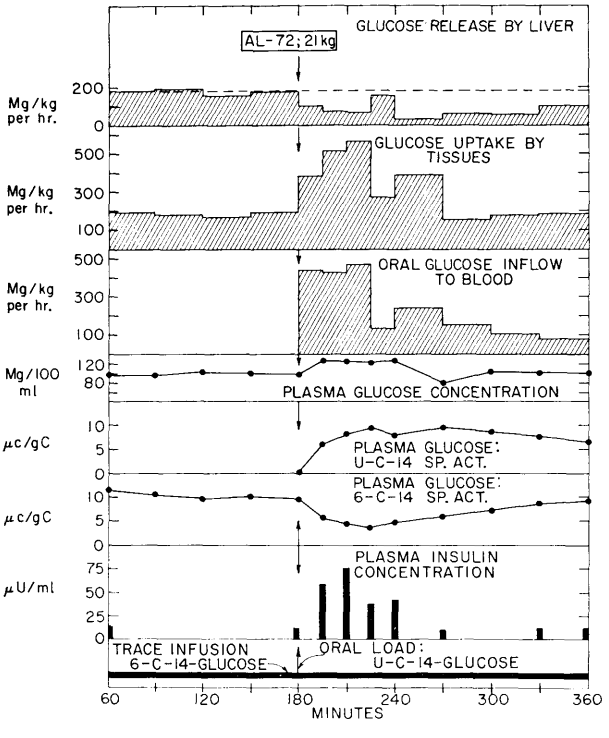

FIG. 1. A typical experiment in which U-C-14-glucose (1 gm./kg.; 11.83 μc/gm. glucose C) was given by stomach tube during continuous intravenous infusion (0.241 μc/min.) of 6-C-14-glucose in trace amount. A priming dose (29.2 μc) of 6-C-14-glucose in trace amount was given at zero time. The dashed line in the "glucose release by liver" panel represents the mean release rate during the control period.

Table 2 gives a summary of the findings for the four oral glucose load experiments, emphasizing the reductions in hepatic glucose release and the increases in glucose uptake as averaged over the period of active glucose absorption, usually three hours. It includes, for comparison, a row of figures which were obtained in previous experiments,[2] in which insulin was given by peripheral vein along with enough glucose to prevent changes in plasma glucose concentration.

Table 3 records the amounts of C-14 found in carbon atoms other than carbon 6 of the circulating glucose, during the continuous intravenous infusion of glucose-6-C-14 prior to oral U-C-14-glucose administration. The first line includes added observations made in a control experiment after an unlabeled glucose load was administered; this forms the basis for using C-14 recycling corrections based on the period prior to the oral load as described in the section on Methods.

Figure 2 shows plasma glucose concentration, and plasma glucose C-14 content in a control experiment in which no intravenous C-14-glucose was given, but in which 6-C-14-glucose was given as the oral glucose load. Total C-14 in plasma glucose and the C-14 reintroduced into plasma glucose (by glucose resynthesis from three carbon fragments) are shown separately. As shown by the earlier values (prior to seventy-five minutes), less than 6 per cent of the C-14-glucose which was transferred from the gut contents to the peripheral blood arrived there by a pathway involving fragmentation and resynthesis.

DISCUSSION

Over the three-hour period required for the absorption of most of an oral glucose load of 1 gm. per kilogram body weight, the liver of the dog has been shown in the present work to release 0.34 gm. per kilogram of new (unlabeled) glucose instead of the 0.63 gm. per kilogram it would otherwise have released. The uptake of glucose from peripheral blood was 1.03 gm. per kilo-

TABLE 1

Unlabeled glucose release by liver to blood, and glucose uptake by tissues from blood, as related to the absorption of an oral glucose load and to the resulting changes in plasma glucose and insulin concentrations

Minutes after oral glucose	AL-73				AL-72				AL-71				AL-66			
	μU./ml. Ins.	mg. per cent Pl. Gl.	mg./kg./hr. Glucose flow L*	R†	U‡	μU./ml. Ins.	mg. per cent Pl. Gl.	mg./kg./hr. Glucose flow L	R	U	μU./ml. Ins.	mg. per cent Pl. Gl.	mg./kg./hr. Glucose flow L	R	U	μU./ml. Ins.	mg. per cent Pl. Gl.	mg./kg./hr. Glucose flow L	R	U
(Control)			(0	266	266)			(0	184	184)			(0	211	211)			(0	182	182)
0	12	96				12	99				11	103				13	100			
0-15			326	152	295			439	103	386			8	193	189 §			34	162	185
15	26	119				57	128				15	100				13	98			
15-30			334	166	390			428	76	519			8	193	189			26	171	174
30	28	133				74	125				16	106	20	104						
30-45			561	156	634			471	74	545			27	178	208 §			83	167	245
45	25	137				36	121				14	105				17	108			
45-60			522	80	657			131	163	273			27	178	208			73	246	284
60	37	133				41	125				10	104				17	110			
60-90			240	120	488			241	29	389			92	187	277			357	96	447
90	18	103				8	79				13	104				15	116			
90-120			248	77	403			153	68	159			304	123	294			75	132	258
120	10	88				—	103				30	140				14	98			
120-150			74	197	239			103	67	178			382	86	522			237	123	335
150	11	92				11	100				23	126				29	114			
150-180			96	260	341			79	104	182			514	48	597			237	123	335
180	11	98				9	100				21	114				12	107			
180-210													84	87	273			179	96	288
210											7	88				—	—			
210-240													130	63	190			179	96	288
240											8	98				—	—			

*Load entry into peripheral blood.
†Release by liver of unlabeled glucose.
‡Uptake of glucose from peripheral blood.
§Mean over the two periods.

TABLE 2

Changes in glucose release by liver and glucose uptake by tissues after administration of an oral glucose load

Dog	Prior to load; glucose turnover (mg./kg./hr.)	Mean decrease in glucose production (a) (mg./kg./hr.)	Per cent	Mean increase in plasma glucose uptake (b) (mg./kg./hr.)	Per cent of glucose homeostasis contributed by decreased production $\frac{100\ a}{a + b}$	Per cent of oral glucose load reaching peripheral circulation	Absorption time period included after oral glucose (min.)
AL-73	266	111	42	144	44	77	0-180
AL-72	184	105	57	111	51	66	0-180
AL-71*	211	112	53	148	43	75	60-240
AL-66†	182	52	29	117	31	69	0-240
Means	211	95	45	132	42	72	
Previous findings (for comparison)‡ Mean:	200§	125‖	63‖	393‖	25		
Range:	165-247	100-143	58-65	333-463	18-28		

*Beginning of load absorption delayed; dog restrained lying on its side.
†Slow initial load absorption and interruption of absorption between 90 and 120 minutes (reflux of duodenal contents to stomach?); dog restrained lying on its side.
‡B-50, B-51, B-58 and B-60 of a previous publication[2]; these dogs received 0.1 to 0.2 U./kg. insulin per hour along with enough glucose (both insulin and glucose by peripheral vein) to maintain unchanged plasma glucose concentration. See text for discussion.
§Prior to intravenous insulin and glucose.
‖During intravenous insulin and glucose.

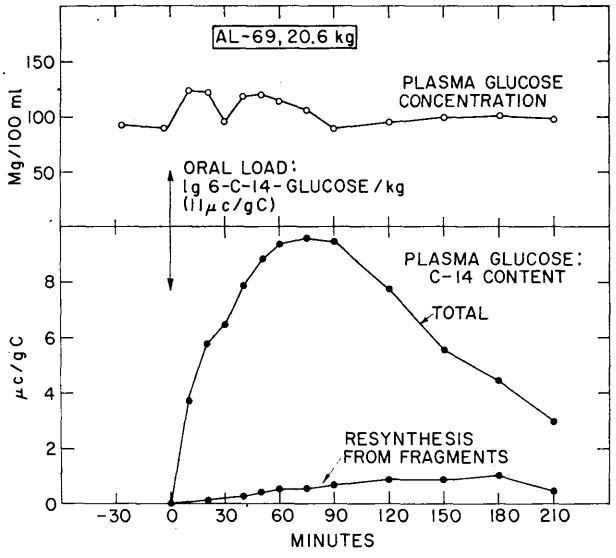

FIG. 2. A control experiment in which 6-C-14-glucose was given in bulk amount by stomach tube. The C-14 content of plasma glucose is expressed as μc C-14 per gram of plasma glucose carbon. Calculation of the amount of C-14 re-introduced into glucose by resynthesis of glucose from C-14 fragments (i.e. 4/3 E) is described in the text. The absorbed C-14 lactate derived in small yield from the oral C-14 glucose on its passage through the gut wall into portal vein blood probably contributes to this resynthesis, but a large share of the C-14 is contributed by the same recycling processes which are evident when 6-C-14-glucose is given by peripheral vein (see text and table 3).

TABLE 3

Recycling of C-14 back into plasma glucose during intravenous 6-C-14-glucose infusion

Infusion time (minutes)	E* in μc/gm.C				
	60	90	Mean 120-180	330	360
AL-72 (Control)†	.28	.03	.39	.44	.34
AL-66	.54	.44	.63	—	—
AL-71	.22	.21	.29	—	—
AL-73	.07	—	.58	—	—
AL-72	.30	.46	.36	—	—

*Glucosotriazole (carbon 1 through 6) specific activity less dimedon (carbon 6) specific activity, each expressed as μc C-14/gm. total glucose carbon. The use of the value E, which is a measure of the recycling of C-14 contained in metabolic fragments back into the glucose output of the liver, is described in the text. For the 120 to 180-minute period the mean total C-14 in plasma glucose was about 10 μc/gm. carbon. For reasons given in the text, an E value of 0.45 μc/gm.C at this time means that 6 per cent of the total C-14 in plasma glucose was recycled C-14.

†In this experiment the 6-C-14-glucose infusion was continued after an *unlabeled* oral glucose load was given at 180 minutes; the load was absorbed as usual during the 180 to 360-minute period as shown by a peak in plasma glucose-concentration, and by an increased total glucose input rate (decline in plasma glucose specific activity).

gram instead of the 0.63 gm. per kilogram it would otherwise have been. Since glucose release was lessened by 0.29 gm. per kilogram and glucose uptake was increased by 0.40 gm. per kilogram, it may be said from these observations that roughly 42 per cent of the total force toward homeostasis was exerted on glucose production and about 58 per cent on glucose uptake.

Endogenously secreted insulin may be somewhat more effective in decreasing glucose release (relative to increasing glucose uptake from peripheral blood) than is insulin administered by peripheral vein; this conclusion was reached earlier by Madison et al.[9] from other evidence. The present evidence for this is complicated by the fact that in the present experiments the amount of insulin secreted was sufficient to decrease unlabeled glucose release by only 97 mg. per kilogram per hour whereas in previously reported experiments[2] we administered enough insulin (along with enough glucose to prevent hypoglycemia) to decrease glucose release by 125 mg. per kilogram per hour. Nevertheless the increase in glucose uptake which occurred simultaneously was so much greater (table 2) when insulin was given by peripheral vein (393 mg./kg. per hour) than when insulin was endogenously secreted (132 mg./kg. per hour) that it seems quite likely that the conclusion is justified. Decreased glucose release accounted for 42 per cent of the homeostatic response in the present experiments whereas it accounted for 25 per cent of the response in the previous experiments in which insulin was given by peripheral vein (table 2). This difference may well be due to the fact that endogenous insulin passes first through the liver where some is extracted, leaving less for distribution to peripheral tissues. As has been reported by others,[3,4] it has been found (unpublished experiments) in this laboratory also that more insulin secretion is evoked by an oral glucose load than is evoked when the same amount of glucose is given by way of a peripheral vein.

Experiments in which hepatic blood flow and glucose concentration differences (between portal and hepatic vein blood) are measured[9,10] emphasize the over-all role of the liver in glucose homeostasis. Such measurements sum together the decrease in hepatic glucose production brought about by insulin, and the increase in hepatic glucose uptake brought about by insulin and by the elevated blood glucose concentration. In the present experiments, some of the glucose absorbed from the gut failed to reach the peripheral circulation because it was removed on its first pass, in portal vein blood,

through the liver. Total glucose uptake (which includes hepatic uptake) calculated as it was from the glucose disappearing from the peripheral blood, was thus somewhat underestimated, and at the same time not all of the absorption of the U-C-14-glucose load was measured by observing the influx of U-C-14-glucose into the peripheral blood. About 72 per cent (66 to 77 per cent) of the administered oral glucose was seen to enter the peripheral circulation; other evidence is called upon to assess the meaning of this observation. In the experiments of Kiyasu, Katz and Chaikoff,[11] about 88 per cent of the C-14 found in portal vein blood during the absorption of U-C-14-glucose was present as glucose; much of the other 12 per cent was lactate, formed from the glucose during its passage through the gut wall. In the present experiments, then, 16 per cent (88 less 72 per cent) of the load is unaccounted for; this is an amount which may have been taken up by liver as glucose on its first pass through via the portal vein. However, it is likely that at least some of this 16 per cent of the U-C-14-glucose load was unabsorbed or was converted to gut tissue constituents on passage of the glucose through the gut wall.

Some years ago it was claimed by Hestrin-Lerner and Shapiro[12,13] that an unidentified metabolite, rather than glucose, was transmitted to the blood from the gut during glucose absorption. However metabolites other than glucose were shown subsequently, by several groups, to be present in quite small amount, the major one being lactate.[11,14] Nevertheless, in a later communication, Tzur and Shapiro[15] questioned the significance of the findings of Taylor and Langdon[16] who found, after oral 1-C-14-glucose administration, that 76 to 91 per cent of the C-14 deposited in liver glycogen was still in carbon 1 of the glucosyl residues. They did so on the ground that the pentose shunt in the gut tissue may have eliminated as CO_2 most of the C-14 from a major portion of the incoming 1-C-14-glucose. They felt then that this major portion might still have been fragmented and reconverted to glucose without the appearance of the expected amount of C-14 in glycogen in locations aside from carbon 1.

The present findings speak against this argument. Glucose labeled in carbon 6 has been shown to give rise to circulating glucose labeled in carbon 6. The randomization was not much, if any, greater than was the case when 6-C-14-glucose was given by way of a peripheral vein. Furthermore, nearly three quarters of the oral glucose load has been shown to reach the peripheral blood by way of this route, which does not involve randomization of the label of the oral glucose load.

During the oral glucose tolerance test, just as in the intravenous test, the release of endogenously produced glucose is not zero and is not constant. Thus a possible advantage of the oral test in terms of ease of interpretation is not realized. As has been known for a long time, the results of the oral test can be influenced by delayed, interrupted, or slowed absorption of the glucose load. In the normal dog it has been observed in the presently reported and other experiments in this laboratory that prompt absorption of an oral load was obtained if the dog was unrestrained, or was kept standing upright in a harness after administration of glucose, but not always if the dog was kept lying on its side during the absorption period.

The glucose tolerance test is a useful empirical indicator of abnormalities in carbohydrate metabolism. It may be the case that an impairment of the decrease in glucose release by the liver is always exactly paralleled by an impairment of the increase in glucose uptake which occurs during the test. Until this is established it is not safe to conclude that an impaired glucose tolerance always indicates an inadequate increase in glucose uptake, because a considerable part of the normal response to the test consists of a decrease in the release of new glucose by the liver.

ACKNOWLEDGMENT

The investigations carried out at Brookhaven National Laboratory were supported by the U. S. Atomic Energy Commission.

The investigations carried out at New York University School of Medicine were supported by Research Grants A-113 (C13-15) and AM 10188-01, 02 from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service, and by Grants P-207 (E,F,G) from the American Cancer Society. Part of the investigation was supported by U. S. Public Health Service Research Career Program Award K_3GM-3368-06, 07, 08 to N. Altszuler.

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