THE PHYSIOLOGICAL SIGNIFICANCE OF THE SECRETION OF ENDOGENOUS INSULIN INTO THE PORTAL CIRCULATION. IV. HEPATIC UPTAKE OF GLUCOSE DURING GLUCOSE INFUSION IN NON-DIABETIC DOGS*

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(Submitted for publication February 15, 1961; accepted May 18, 1961)

Recent studies from this laboratory (1) have shown that insulin has an immediate and profound effect upon net hepatic glucose balance. When insulin was administered at a rate (2) estimated to minimize the counter-regulatory responses to hypoglycemia, the decline in blood glucose which ensued was largely the consequence of a diminished hepatic release of glucose (1).

Since, under physiologic circumstances, endogenous insulin secretion is stimulated by the rising blood glucose concentration (3, 4) which follows a carbohydrate meal, the effect of insulin in regulating hepatic glucose metabolism is best assessed in the presence of a glucose load. Whether or not hyperglycemia, with its attendant release of endogenous insulin, results in a decrease or cessation of hepatic glucose output has been a controversial subject (5–13). However, in all but one of the previous studies (5), the conclusions were based upon inferential data, since net hepatic glucose balance was not measured.

The present studies were undertaken to determine the effect of hyperglycemia and the concomitant release of endogenous insulin upon hepatic glucose metabolism. Hyperglycemia was produced by the intravenous infusion of glucose. The rate of glucose administration was varied in order to define better some of the factors that control hepatic glucose output. Dogs with complete end-to-side portacaval shunts were used, since this preparation separates the circulation of the liver from that of the remainder of the splanchnic bed and thereby permits measurement of hepatic rather than splanchnic glucose balance (1).

* This work was supported by research grants from the United States Public Health Service (A-4236, H-3439), the Upjohn Company and the American Heart Association. An abstract has been published in J. Lab. clin. Med. 1959, **54**, 799. Presented in part before the American Diabetes Association, Miami Beach, Fla., June 11, 1960.

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METHODS AND PROCEDURE

Twenty-two studies were performed in dogs in which end-to-side portacaval shunts had been performed at least 2 weeks earlier. The dogs were anesthetized with Nembutal (25 mg per kg i.v.) 15 hours after food had been removed from their cages. Previously they had been maintained on a ration in which approximately 50 per cent of the total calories was derived from carbohydrate, 20 to 30 per cent from protein, and the remainder from fat. Hepatic venous blood samples were collected through a cardiac catheter inserted deep into a hepatic vein under fluoroscopic control. Position of the catheter was checked at intervals during each experiment. Arterial blood samples were obtained through a Cournand needle placed in a femoral artery.

Hepatic blood flow and the concentration of glucose in arterial and hepatic venous blood were determined at 10-minute intervals throughout the study. Hepatic blood flow was estimated by the clearance-and-extraction method of Bradley, Ingelfinger, Bradley and Curry (14), with I^{131}-labeled rose bengal as the extractable material (15). Blood glucose was determined in triplicate on each blood sample by the Somogyi copper iodometric method (16,17). The methods used in this laboratory have been described in detail in a previous publication (1). Hepatic glucose balance in milligrams per minute at each 10-minute interval was calculated as the product of the estimated hepatic blood flow and the hepatic venous-femoral arterial glucose concentration difference.

Two to four measurements of hepatic glucose output were obtained during a control period. In 11 studies, changes in hepatic glucose balance were then followed during the administration of a constant infusion of glucose into a hind leg vein. In some studies, after the glucose was stopped, additional measurements were obtained during the "recovery" period.

In 11 other studies the effects of insulin, administered prior to and during the glucose infusion, on hepatic glucose balance were determined. Glucagon-free insulin[1] was administered slowly by constant intravenous infusion for 30 to 60 minutes after control measurements had been made. Glucose was then infused, together with the insulin, for another 60 to 80 minutes.

RESULTS

1. *Effect on hepatic glucose balance*

A. Glucose infusion. In each of the 11 dogs glucose infusion produced a fall in hepatic glucose output (Tables I and II). Within 10 minutes mean hepatic glucose output fell from 50.7 to 27.6 mg per minute. This 46 per cent decrease in hepatic output of glucose was associated with a rise in mean arterial glucose concentration of only 9.4 mg per 100 ml—from 82.1 to 91.5 mg per 100 ml. By 50 minutes, mean hepatic glucose output fell to only 1.4 mg per minute, a 97 per cent change from the mean control value. From 60 to 90 minutes, hepatic glucose output ceased; instead, the liver was *extracting* an average of 20.2 mg per minute during this time (Table I). This represents a net conservation of glucose by the liver of 70.9 mg per minute.

A net uptake or positive balance of glucose across the liver was observed in 7 of the 11 dogs (Figure 1). In the other 4 animals, although net uptake of glucose by the liver did not occur, hepatic glucose output fell markedly during the infusion, averaging 5.3 mg per minute 90 minutes after glucose was started, a 91.2 per cent decrease from the mean control output of 60.5 mg per minute.

Inspection of the data (Table I) obtained from 11 dogs suggests that a positive glucose balance across the liver is related to the rate at which arterial glucose concentration increased. In the 7 dogs in which net hepatic uptake of glucose was observed, mean arterial glucose concentration increased 33 mg per 100 ml by 30 minutes and 65.5 by 90 minutes after starting glucose. By contrast, in the 4 dogs that did not attain positive hepatic glucose balance, arterial glucose concentration increased only 10 mg per 100 ml at 30 minutes and 32.2 at 90 minutes. In general, the more rapid rise in arterial glucose concentration in the "uptake" dogs was attributable to the infusion of larger glucose loads (Table I) and, more specifically, to the greater extent to which the infused loads exceeded the control hepatic glucose output. In considering the entire group of 11 animals, the quantity of glucose infused per minute was 3.5 to 5.8 times greater than the control hepatic glucose output during the 90 minutes of infusion in the "uptake" dogs, whereas it was only 0.9 to 2.4 times greater than control hepatic glucose output in the "non-uptake" dogs.

The mean arterial glucose concentration at which net uptake of glucose by the liver was first observed was 115.6 mg per 100 ml (Table III), a value 36.3 mg higher than the mean control. A rising arterial glucose concentration was not prerequisite for a positive hepatic glucose balance, since net uptake not only continued when arterial glucose concentration had reached a plateau, but also when arterial glucose concentration was falling (Table I, Dogs 522, 525, 610).

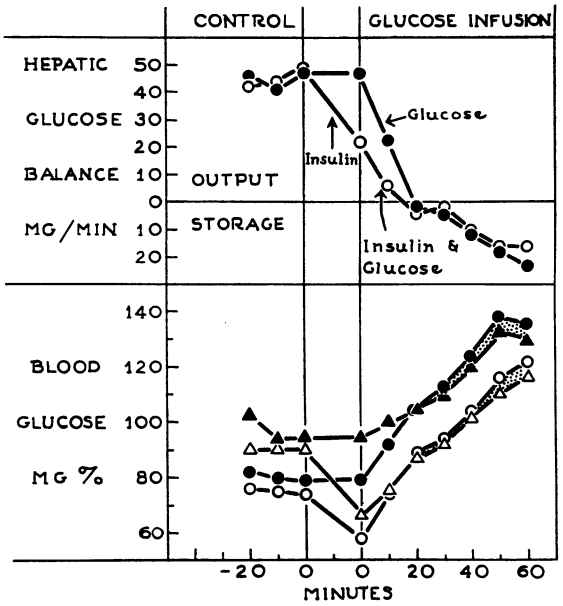

FIG. 1. COMPARISON OF MEAN CHANGES IN HEPATIC AND ARTERIAL GLUCOSE CONCENTRATIONS, AND HEPATIC GLUCOSE BALANCE IN DOGS DEMONSTRATING A NET HEPATIC UPTAKE OF GLUCOSE DURING GLUCOSE INFUSION ALONE AND DURING INSULIN AND GLUCOSE INFUSIONS. Solid symbols used for data in dogs receiving only glucose; open symbols for dogs receiving insulin and glucose infusions. For blood glucose data, triangles refer to glucose concentration in hepatic venous blood, circles to glucose concentration in arterial blood.

[1] We are indebted to Dr. W. R. Kirtley of the Eli Lilly Co. for the generous supply of glucagon-free insulin.

TABLE I

Effect of glucose infusion upon hepatic glucose balance *

Dog	Weight		Control values −30	−20	−10	0	Mean control	Time during and after glucose infusion 10	20	30	40	50	60	70	80	90	100	110	120
no.	*kg*																		
35	16.8	EHBF		178	176	188	181	177	163	207	187	174	187	183	179	175			
		HV		144.4	122.1	120.4	129.0	123.0	133.4	133.7	139.9	146.4	143.3	137.3	130.8	126.6			
		A		98.4	98.1	99.8	98.8	104.9	112.8	117.0	126.3	135.1	132.0	128.9	127.5	124.9			
		HV-A		46.0	24.0	20.6	30.2	18.1	20.6	16.7	13.6	11.3	11.3	8.4	3.3	1.7			
		HGB		81.9	42.2	38.7	54.3	32.0	33.6	34.6	25.4	19.7	21.1	15.4	5.9	3.0			
		Glucose						←50 mg/min→											
36	25.9	EHBF		160	187	262	203	229	191	237	164	183	165	181	198	211	213	231	229
		HV		116.5	137.6	112.0	122.0	108.6	110.3	117.0	120.4	120.7	121.0	130.0	133.1	138.7	126.9	112.5	104.1
		A		89.4	91.4	89.7	90.2	88.8	90.0	89.7	99.8	106.3	113.1	121.8	133.4	138.7	119.6	105.5	99.5
		HV-A		27.1	46.2	22.3	31.9	19.8	20.3	27.3	20.6	14.4	7.9	8.2	+0.3	0	7.3	7.0	4.6
		HGB		59.6	86.4	58.4	68.1	45.3	38.8	56.2	33.8	26.4	13.0	14.8	+0.6	0	15.5	16.2	10.5
		Glucose						←50 mg/min→			←100 mg/min→			←150 mg/min→			←None→		
319	17.2	EHBF		170	147	142	153	134	125	143	149	140	145	149	129	158	169		
		HV		120.7	117.4	111.9	116.7	108.3	112.2	110.2	113.5	111.9	112.7	109.1	110.8	109.1	101.4		
		A		85.5	84.9	83.8	84.7	82.5	84.7	84.4	92.1	96.5	99.0	100.1	100.9	99.2	93.7		
		HV-A		35.2	32.5	28.1	32.0	25.8	27.5	25.8	21.4	15.4	13.7	9.1	9.9	9.9	7.7		
		HGB		59.8	47.8	39.9	49.2	34.6	34.4	36.9	31.9	21.6	19.9	13.6	12.8	15.6	13.0		
		Glucose						←50 mg/min→			←100 mg/min→			←150 mg/min→					
513	19.0	EHBF	202	210	196	201	202	212	223	223	234	226	223	191	186	187	188		
		HV	111.8	111.8	108.5	102.1	108.6	101.8	99.4	100.2	100.4	101.3	113.4	121.8	122.6	117.7	106.7		
		A	75.6	74.8	74.8	69.9	73.8	84.5	92.6	96.4	98.0	99.1	117.2	121.2	121.0	113.7	104.0		
		HV-A	36.2	37.0	33.7	32.2	34.8	17.3	6.8	3.8	2.4	2.2	+3.8	0.6	1.6	4.0	2.7	5.1	
		HGB	73.1	77.7	66.1	64.7	70.4	36.7	15.2	8.5	5.6	5.0	+8.5	1.1	3.0	7.5	5.1		
		Glucose						←100 mg/min→					←200 mg/min→						
126	19.1	EHBF		200	206	200	202	208	205	277	250	329	298	372	366	298	309		
		HV		91.7	88.5	90.5	90.2	91.7	93.1	94.0	93.1	92.2	100.0	104.2	108.8	120.5	124.8		
		A		85.1	84.8	85.1	85.0	87.7	92.2	96.5	96.2	97.1	106.0	111.0	119.0	131.9	136.8		
		HV-A		6.6	3.7	5.4	5.2	4.0	0.9	+2.5	+3.1	+4.9	+6.0	+7.2	+10.2	+11.4	+12.0		
		HGB		13.2	7.6	10.8	10.5	8.3	1.9	+6.9	+7.8	+16.1	+17.9	+26.8	+37.3	+34.0	+37.1		
		Glucose						←50 mg/min→			←100 mg/min→				←150 mg/min→				
312	12.4	EHBF			442	463	453	419	379	410	399		402	428	342	369	403	267	267
		HV			74.8	69.3	72.1	76.6	71.5	72.1	80.2		97.4	99.7	108.6	113.9	101.3	80.5	71.3
		A			62.9	58.7	60.8	65.1	63.8	62.6	76.3		96.0	104.7	115.5	123.3	101.3	81.3	70.2
		HV-A			11.9	10.6	11.3	11.5	7.7	9.5	3.9		1.4	+5.0	+6.9	+9.4	0	+0.8	1.2
		HGB			52.6	49.1	50.9	48.2	29.2	39.0	15.6		5.6	+21.4	+23.6	+34.7	0	+2.1	3.2
		Glucose						←50 mg/min→			←100 mg/min→			←150 mg/min→			←None→		

* Abbreviations are as follows: EHBF, estimated hepatic blood flow in ml/min; HV, hepatic venous glucose concentration in mg%; A, arterial glucose concentration in mg %; HV-A, hepatic venous minus arterial glucose concentration in mg %; HGB, hepatic glucose balance in mg/min. Figures without preceding sign indicate net hepatic glucose output. Those preceded by + indicate net hepatic uptake of glucose.

TABLE I—(*Continued*)

Dog	Weight		Control values				Mean control	Time during and after glucose infusion											
			−30	−20	−10	0		10	20	30	40	50	60	70	80	90	100	110	120
no.	*kg*																		
326	17.3	EHBF		207	250	306	254	348	333	312	392	452	521	527	533	491	469	476	500
		HV		126.1	107.7	103.7	112.5	99.7	103.0	111.3	130.0	145.4	146.4	147.3	168.5	165.2	117.9	77.4	55.4
		A		89.0	90.1	85.6	88.2	95.0	102.7	111.3	133.3	151.2	161.8	172.4	177.1	177.4	114.8	74.1	58.4
		HV-A		37.1	17.6	18.1	24.3	4.7	0.3	0	+3.3	+5.8	+15.4	+25.1	+8.6	+12.2	3.1	3.3	+3.0
		HGB		76.8	44.0	55.4	58.7	16.4	1.0	0	+12.9	+26.2	+80.2	+132.3	+45.9	+59.9	14.5	15.7	+15.0
		Glucose						←——100 mg/min——→			←——200 mg/min——→			←——300 mg/min——→			←——None——→		
327	25.9	EHBF		397	382	418	399	309	357	327	380	312	370	381	381	346	321	323	318
		HV		96.4	98.9	97.6	97.6	99.7	95.8	92.5	99.9	105.5	108.8	113.7	122.9	125.9	104.3	87.7	78.8
		A		83.9	82.1	83.9	83.3	88.7	91.3	93.3	102.7	110.1	115.5	124.9	133.1	140.7	106.3	89.5	79.3
		HV-A		12.5	16.8	13.7	14.3	11.0	4.5	+0.8	+2.8	+4.6	+6.7	+11.2	+10.2	+14.8	+2.0	+1.8	+0.5
		HGB		49.6	64.2	57.3	57.0	42.9	16.0	+2.6	+10.6	+14.4	+24.8	+42.7	+38.9	+51.2	+6.4	+5.8	+1.6
		Glucose						←——100 mg/min——→			←——200 mg/min——→			←——300 mg/min——→			←——None——→		
522	18.2	EHBF	202	185	189	213	197	210	210	202	212	221	230	240	249	258	259	215	228
		HV	107.1	119.1	101.7	102.5	107.6	116.0	134.9	155.3	191.3	200.4	201.2	195.1	193.3	190.2	185.4	182.1	174.7
		A	83.4	82.6	80.3	79.8	81.5	109.9	142.5	165.5	197.4	204.5	207.6	205.5	210.1	208.6	203.5	198.9	191.0
		HV-A	23.7	36.5	21.4	22.7	26.1	6.1	+7.6	+10.2	+6.1	+4.1	+6.4	+10.4	+16.8	+18.4	+18.1	+16.8	+16.3
		HGB	47.9	67.6	40.5	48.4	51.1	12.8	+16.0	+20.6	+12.9	+9.1	+14.7	+25.0	+41.8	+47.5	+46.9	+36.1	+37.2
		Glucose						←——————————————————235 mg/min——————————————————→											
525	20.0	EHBF	208	188	213	222	208	220	255	301	252	273	260	253	204	213	193	159	146
		HV	92.8	89.3	90.5	105.6	94.6	104.9	112.6	120.5	120.0	116.6	111.8	107.9	104.4	104.4	76.6	56.5	52.6
		A	74.6	72.9	72.9	74.2	73.7	100.4	118.8	126.7	125.7	122.8	117.6	115.1	110.4	112.6	71.2	49.1	36.7
		HV-A	18.2	16.4	17.6	31.4	20.9	4.5	+6.2	+6.2	+5.7	+6.2	+5.8	+7.2	+6.0	+8.2	5.4	7.4	15.9
		HGB	37.9	30.8	37.5	69.7	44.0	9.9	+15.8	+18.7	+14.4	+16.9	+15.1	+18.2	+12.2	+17.5	10.4	11.8	23.2
		Glucose						←——————————————————235 mg/min——————————————————→									←——None——→		
610	25.0	EHBF	271	289	262	311	283	269	270	284	370	305	332	224	214	271	260	163	171
		HV	99.7	96.0	96.7	97.7	97.5	105.2	118.3	126.7	133.9	139.9	140.6	132.9	122.5	111.8	85.6	71.7	68.9
		A	83.8	82.3	81.3	82.1	82.4	99.2	119.8	130.0	141.4	146.3	147.1	140.1	127.7	118.8	79.1	61.3	54.6
		HV-A	15.9	13.7	15.4	15.6	15.2	6.0	+1.5	+3.3	+7.5	+6.4	+6.5	+7.2	+5.2	+7.0	6.5	10.4	14.3
		HGB	43.1	39.6	40.3	48.5	42.9	16.1	+4.1	+9.4	+27.8	+19.5	+21.6	+16.1	+11.1	+18.7	16.9	17.0	24.5
		Glucose						←——————————————————235 mg/min——————————————————→									←——None——→		
Mean																			
	20.6	EHBF		219	241	266	248	256	247	266	272	263	285	284	271	271			
		HV		111.2	104.0	101.2	104.4	103.2	107.7	112.1	120.2	128.2	127.0	127.1	129.6	129.2			
		A		84.4	82.2	81.2	82.1	91.5	101.1	106.7	117.2	127.2	128.5	131.4	134.7	135.2			
		HV-A		26.8	21.8	20.0	22.3	11.7	6.6	5.4	3.0	1.0	+1.5	+4.3	+5.1	+6.0			
		HGB		55.7	45.2	49.2	50.7	27.6	12.2	10.6	3.4	1.4	+11.3	+21.6	+17.3	+21.6			
		Glucose						←——112 mg/min——→			←——152 mg/min——→			←——197 mg/min——→					

TABLE II

Changes in hepatic glucose balance from control during a glucose infusion

Dog no.	Mean control	Decrease in hepatic glucose output from control, mg/min*									
		Minutes after start of glucose infusion									
		10	20	30	40	50	60	70	80	90	100
35	54.3	22.3	20.7	19.7	28.9	34.6	33.2	38.9	48.4	51.3	
36	68.1	22.8	29.3	11.9	34.3	41.7	55.1	53.3	68.7	68.1	
319	49.2	14.6	14.8	12.3	17.3	27.6	29.3	35.6	36.4	33.6	
513	70.4	33.7	55.2	61.9	64.8	65.4	78.9	69.3	67.4	62.9	65.3
126	10.5	2.2	8.6	17.4	18.3	26.6	28.4	37.3	47.8	44.5	47.6
312	50.9	2.7	21.7	11.9	35.3		45.3	72.3	74.5	85.6	
326	58.7	42.3	57.7	58.7	71.6	84.9	138.9	191.0	104.6	118.6	
327	57.0	14.1	41.0	59.6	67.6	71.4	81.8	99.7	95.9	108.2	
522	51.1	38.3	67.1	71.7	64.0	60.2	65.8	76.1	92.9	98.6	
525	44.0	34.1	59.8	62.7	58.4	60.9	59.1	62.2	56.2	61.5	
610	42.9	26.8	47.0	52.3	70.7	62.4	64.5	59.0	54.0	61.6	
Mean		23.1	38.5	40.1	47.3	49.3	62.0	72.3	68.0	72.3	
p		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	

* Value for hepatic glucose balance added to control hepatic glucose output where a net uptake of glucose by the liver was observed.

When the glucose infusion was stopped, hepatic glucose output was usually resumed as the arterial glucose concentration approached or reached control levels (Table I), but in none of the 6 dogs in which hepatic glucose balance was measured during a 30-minute recovery period did hepatic glucose output return to control values. This was particularly striking in 4 animals (Dogs 326, 327, 525, 610) in which hepatic glucose output averaged only 7.8 mg per minute at a time when mean arterial glucose levels had fallen to 57.3 mg per 100 ml, a value 24.6 mg below their control levels. Indeed, in Dogs 326 and 327, net hepatic glucose uptake was still apparent when the arterial glucose level was lower than control.

B. Insulin and glucose infusions. Hepatic glucose output decreased below control values in all 11 dogs during the period of glucose and insulin infusion. Net hepatic uptake of glucose was observed in 6 of the dogs. Failure of glucose infusions to raise the arterial sugar concentration to preinsulin control values probably accounted for the failure of the other 5 dogs to attain a hepatic uptake of glucose. In these dogs insulin infusion lowered mean arterial glucose concentration from a control value of 83.4 to 59.6 mg per 100 ml. When glucose was added to the insulin infusion, the arterial glucose level increased to an average peak value of only 76.5 mg per 100 ml. The detailed data from the 6 animals in which hepatic

TABLE III

Comparison of the arterial glucose concentration, at which net hepatic uptake of glucose was first observed, with control arterial glucose concentration

	Glucose infusion		Insulin and glucose infusion			
	Arterial glucose concentration, mg %					
Dog no.	Mean control	Net hepatic uptake first observed	Dog no.	Mean control	Last value with insulin alone	Net hepatic uptake first observed
126	85.0	96.5	1,219	84.9	80.0	126.3
312	60.8	104.7	15	42.5	26.0	92.0
326	88.2	133.3	119	82.5	67.1	69.7
327	83.3	93.3	624	74.8	54.0	95.8
522	81.5	142.5	717	88.5	65.3	91.4
525	73.7	118.8	722	83.4	58.0	82.3
610	82.4	119.8				
Mean	79.3	115.6		76.1		92.9
SD	±8.3	±16.8		±15.6		±17.3

TABLE IV

Effect of insulin and glucose infusions upon hepatic glucose balance *

Dog	Weight		Control values				Mean control	Last value insulin alone	Time during insulin and glucose infusion							
			−30	−20	−10	0			10	20	30	40	50	60	70	80
no.	*kg*															
15	15.4	EHBF		290	332	308	310	236	230	245	267	224	230	257		
		HV		56.0	52.0	52.6	53.5		44.6	57.1	60.3	87.4	114.8	140.2		
		A		43.1	43.4	41.1	42.5	26.0	40.3	54.3	58.3	92.0	118.5	146.8		
		HV-A		12.9	8.6	11.5	11.0		4.3	2.8	2.0	+4.6	+3.7	+6.6		
		HGB		37.4	28.6	35.4	33.8		9.9	6.9	5.3	+10.3	+14.7	+17.0		
		Insulin						←0.026 U/min→								
		Duration insulin alone						←40 min→								
		Glucose							←75 mg/min→			←200 mg/min→				
119	25.5	EHBF		521	512	497	510	606	609	533	583	596	712	664		
		HV		98.0	96.2	94.0	96.1		68.5	72.0	73.7	77.4	82.0	82.0		
		A		85.3	81.1	81.1	82.5	67.1	69.7	74.3	72.8	81.4	85.7	86.5		
		HV-A		12.7	15.1	12.9	13.6		+1.2	+2.3	0.9	+4.0	+3.7	+4.5		
		HGB		66.0	77.3	64.1	69.1		+7.3	+12.3	5.3	+23.8	+26.3	+29.9		
		Insulin						←0.043 U/min→								
		Duration insulin alone						←40 min→								
		Glucose							←100 mg/min→			←200 mg/min→				
1219	18.2	EHBF		166	164	193	174	253	248	275	236	217	277	267		
		HV		100.4	104.7	100.7	101.9		83.6	93.3	100.7	104.4	120.0	130.0		
		A		85.9	84.5	84.2	84.9	80.0	85.6	92.5	99.6	102.1	126.3	138.6		
		HV-A		14.5	20.2	16.5	17.1		+2.0	0.8	1.1	2.3	+6.3	+8.6		
		HGB		24.1	33.1	31.8	29.7		+5.0	2.2	2.6	5.0	+17.4	+23.0		
		Insulin						←0.045 U/min→								
		Duration insulin alone						←40 min→								
		Glucose							←100 mg/min→			←200 mg/min→				
722	27.3	EHBF			302	284	293	344	300	293	201	233	222	223	223	
		HV			100.8	99.4	100.1		80.5	88.7	90.1	93.0	93.3	98.1	94.9	
		A			84.7	82.1	83.4	58.0	82.3	90.3	91.7	95.7	98.4	99.2	99.4	
		HV-A			16.1	17.3	16.7		+1.8	+1.6	+1.6	+2.7	+5.1	+1.1	+4.5	
		HGB			48.6	49.1	48.9		+5.4	+4.7	+3.2	+6.3	+11.3	+2.5	+10.0	
		Insulin						←0.046 U/min→								
		Duration insulin alone						←60 min→								
		Glucose							←235 mg/min→							

* See Table I for abbreviations.

TABLE IV—(*Continued*)

Dog	Weight		Control values −30	−20	−10	0	Mean control	Last value insulin alone	Time during insulin and glucose infusion 10	20	30	40	50	60	70	80
no.	*kg*															
624	15.0	EHBF	231	226	229	256	236	267	321	307	276	279	267	221		
		HV	93.1	90.8	86.1	93.4	90.9		88.6	92.3	99.1	102.9	107.7	108.0		
		A	76.1	75.6	72.9	74.5	74.8	54.0	76.1	95.8	104.0	108.3	115.8	115.0		
		HV-A	17.0	15.2	13.2	18.9	16.1		12.5	+3.5	+4.9	+5.4	+8.1	+7.0		
		HGB	39.3	34.4	30.2	48.4	38.1		40.1	+10.7	+13.5	+15.1	+21.6	+15.5		
		Insulin						←———	———	———	0.025 U/min	———	———	———→		
		Duration insulin alone						←60 min→								
		Glucose							←———	———	235 mg/min	———	———	———→		
717	25.5	EHBF	292	292	266	318	292	288	284	275	308	259	256	221	190	219
		HV	105.7	109.2	104.4	104.1	105.9		89.2	123.2	138.2	146.8	147.6	147.8	152.7	162.6
		A	91.9	92.5	86.6	83.1	88.5	65.3	91.4	123.7	139.7	147.8	149.7	151.6	158.8	164.6
		HV-A	13.8	16.7	17.8	21.0	17.3		+2.2	+0.5	+1.5	+1.0	+2.1	+3.8	+6.1	+2.0
		HGB	40.3	48.8	47.3	66.8	50.8		+6.2	+1.4	+4.6	+2.6	+5.4	+8.4	+11.6	+4.4
		Insulin						←———	———	———	0.043 U/min	———	———	———	———	———→
		Duration insulin alone						←60 min→								
		Glucose							←———	———	———	235 mg/min	———	———	———	———→
Mean																
	21.2	EHBF		299	301	309	303	332	332	321	312	301	327	309		
		HV		90.9	90.7	90.7	91.4		75.8	87.8	93.7	102.0	110.9	117.7		
		A		76.5	75.5	74.4	76.1	58.4	74.2	88.5	94.4	104.6	115.7	122.3		
		HV-A		14.4	15.2	16.4	15.3		1.6	+0.7	+0.7	+2.6	+4.8	+6.2		
		HGB		42.1	44.2	49.3	45.1		6.5	+3.3	+1.4	+8.9	+16.1	+16.1		
		Insulin						←———	———	———	0.038 U/min	———	———	———→		
		Glucose							←———	163 mg/min	———→	←———	218 mg/min	———→		

glucose uptake occurred are contained in Table IV and Figure 1. After insulin (0.038 U per minute) had been infused for 40 to 60 minutes, mean control arterial glucose concentration fell from 76.1 to 58.4 mg per 100 ml. As in previous studies reported from this laboratory (1), this decline in arterial glucose concentration was associated with a 52 per cent decrease in mean hepatic glucose output—from 45.1 to 21.6 mg per minute. With the addition of the glucose infusion, a further prompt fall in hepatic glucose output, followed by a net hepatic uptake of glucose, was observed. The magnitude of the hepatic uptake of glucose was similar in the dogs that received only glucose and in those to which both insulin and glucose were administered (Figure 1). The major difference between these two groups in which a positive glucose balance across the liver was observed was *the mean concentration of arterial glucose at which net hepatic glucose uptake first occurred.* When glucose alone was infused, net hepatic uptake was noted at a mean arterial glucose concentration of 115.6 mg per 100 ml (Table III); pretreatment with insulin lowered this value to 92.9. Indeed, in Dog 119, net hepatic uptake of glucose occurred at an arterial glucose level of 69.7 mg per 100 ml, a value 12.8 mg lower than control.

The changes in hepatic glucose metabolism observed in the present experiments were attributed solely to alterations in the arterial-hepatic venous glucose concentration differences, since hepatic blood flow did not change significantly during the course of these studies. The development of a positive arterial-hepatic venous glucose concentration difference, at a time when the arterial glucose concentration was rising, cannot be attributed to sampling errors, since positive glucose balance across the liver also occurred at a time when the arterial glucose concentration had reached a plateau or was falling. If any error in sampling existed, it was in the direction of underestimating the fall in hepatic glucose output. Since in these studies glucose was infused into a vein in the hind limb, the concentration of glucose in inferior vena caval blood would be higher than in blood entering or leaving the liver. Should hepatic venous blood be contaminated by regurgitation from the inferior vena cava, a falsely high value for hepatic venous glucose concentration would result.

2. Disposition of the infused glucose load

The extent to which the liver and the peripheral tissues contribute to the disposition of the glucose load can be approximated from the data. The amount of infused glucose remaining in the glucose pool was estimated by multiplying the change in arterial glucose concentration after glucose infusion by the glucose space. For these calculations it was assumed that the glucose space was 30 per cent of the body weight in the dog (1, 18, 19). That portion of the glucose load which disappeared from the glucose pool, as a result of a change in hepatic glucose metabolism during the glucose infusion, was determined as the amount by which hepatic glucose output decreased from control values. The infused glucose not accounted for either by a decrease in hepatic glucose output or by an increase in the glucose pool was assumed to represent the increase in glucose utilization by the peripheral tissues. Since the filtered load of glucose expected at the blood sugar concentrations obtained in these studies was less than the glucose Tm usually observed in dogs (20, 21), significant renal excretion of glucose seems unlikely. Therefore, no correction was made for possible urinary loss of glucose.

These calculated data are contained in Table V. A mean of 13,810 mg of glucose was added to the glucose pool during a 90-minute period of glucose infusion. Approximately one quarter (3,290 mg) remained in the glucose pool at the end of 90 minutes. Of the 10,520 mg which disappeared from the glucose pool, 48 per cent could be attributed to an altered hepatic glucose output and 52 per cent to an increase in peripheral glucose utilization. The proportion of glucose accounted for by the liver and peripheral tissues varied considerably in different studies. In Dog 35, 80 per cent of the utilized glucose was disposed of by the liver and 20 per cent by peripheral tissues, whereas in Dogs 319 and 610, the liver accounted for only 25 per cent and peripheral tissues for 75 per cent of the glucose utilized. The extent to which the liver and the peripheral tissues utilized glucose was related to the load of glucose infused and, more specifically, to the ratio of glucose infused per minute to control hepatic glucose output. When the ratio of glucose load to initial hepatic glucose output was low, a change in hepatic glu-

TABLE V

Disposition of infused glucose

Dog	Weight	Glucose infused in 90 minutes		− Increase in glucose pool		= Glucose utilized		Disposition of glucose utilized: Decrease in hepatic glucose output		Peripheral* utilization		Fraction of glucose accounted for by	
			Total		Total		Total		Total		Total	Liver	Peripheral tissues
no.	*kg*	*mg/10 kg*	*mg*	*mg/10 kg*	*mg*	*mg/10 kg*	*mg*	*mg/10 kg*	*mg*	*mg/10 kg*	*mg*		
35	16.8	2,680	4,500	785	1,315	1,895	3,185	1,520	2,555	375	630	0.80	0.20
36	25.9	3,470	9,000	1,460	3,790	2,010	5,210	1,355	3,510	660	1,700	0.67	0.33
126	19.1	4,190	8,000	1,405	2,685	2,785	5,315	1,090	2,095	1,685	3,220	0.39	0.61
319	17.2	5,230	9,000	430	745	4,800	8,255	1,190	2,045	3,610	6,210	0.25	0.75
513	19.0	6,840	13,000	1,200	2,275	5,640	10,725	2,780	5,275	2,870	5,450	0.49	0.51
327	25.9	6,950	18,000	1,720	4,460	5,230	13,540	2,260	5,850	2,965	7,690	0.43	0.57
312	12.4	7,250	9,000	3,240	4,010	4,010	4,990	2,800	3,470	1,225	1,520	0.70	0.30
610	25.0	8,560	21,150	1,090	2,730	7,470	18,420	1,870	4,670	5,500	13,750	0.25	0.75
326	17.3	10,400	18,000	2,570	4,625	7,830	13,375	4,670	8,095	3,050	5,280	0.60	0.40
525	20.0	10,575	21,150	1,170	2,335	9,405	18,815	2,475	4,945	6,935	13,870	0.26	0.74
522	18.2	11,600	21,150	3,800	6,940	7,800	14,210	3,210	5,860	4,590	8,350	0.41	0.59
Mean	20.6	6,710	13,810	1,595	3,290	5,115	10,520	2,120	4,360	2,990	6,160	0.48	0.52

* Represents increase in peripheral utilization of glucose above control values.

cose output was of major importance in the disposition of a glucose load. With increasing glucose loads, the peripheral tissues played a proportionately greater role.

DISCUSSION

It is apparent that the liver responds promptly and significantly to a glucose load. Within 10 minutes after beginning an intravenous infusion of glucose in 11 dogs, mean hepatic glucose output fell 46 per cent. The mechanisms responsible for this change are apparently sensitive to very small increments of blood sugar, since this 46 per cent decrease in hepatic glucose output was associated with a rise in mean arterial glucose concentration of only 9.4 mg per 100 ml. As glucose infusion continued, a progressive decrease in hepatic glucose output ensued in all the dogs studied, and in 7 dogs a positive glucose balance across the liver, or net hepatic uptake, was observed.

Theoretically, changes in hepatic glucose balance during the administration of a glucose load may be the consequence of one of the following: first, hyperglycemia per se, in the absence of insulin; second, hyperglycemia in the presence of a fixed amount of insulin; finally, increased secretion of endogenous insulin secondary to arterial hyperglycemia.

The first of these possibilities is best assessed in the insulin-deficient diabetic. In both the diabetic human (22–24) and diabetic dog (25, 26), hepatic glucose output was normal or increased despite the presence of arterial hyperglycemia. A decreased hepatic glucose output or net hepatic uptake of glucose was not observed. By contrast, with comparable arterial glucose concentrations, a marked decrease in hepatic glucose output and significant hepatic uptake of glucose are regularly observed in normal dogs. Furthermore, the response of the liver to a glucose load was impaired in dogs made diabetic by partial pancreatectomy and administration of alloxan (26). Thus, the arterial glucose concentration at which the liver stopped putting out glucose and started taking it up was elevated; the more severe the diabetes, the higher the blood glucose level required for hepatic glucose uptake; finally, elevation of blood glucose to as high as 500 mg per 100 ml did not result in hepatic uptake of glucose in some dogs. These observations indicate that hyperglycemia per se, in the absence of insulin, cannot explain the alterations in hepatic glucose balance observed in the present study.

The possibility that hyperglycemia in the presence of a fixed amount of insulin is responsible for the changes in hepatic glucose balance was not assessed in the present studies, since endogenous insulin secretion probably increased during glucose loading (3, 4). Nevertheless, this possibility was suggested by the studies of Soskin, Allweiss and Cohn (27), based on glucose tolerance tests in dogs. In the studies of Soskin and

colleagues, a constant blood sugar was maintained in depancreatized dogs by the constant infusion of both insulin and glucose for at least 1 to 2 hours. When these infusions were continued, the subsequent injection of an additional glucose load resulted in "normal" glucose tolerance tests in most of these animals. Since further secretion of endogenous insulin was impossible, an increase in insulin secretion was not considered necessary for the normal disposition of a glucose load. When the pancreas was left intact but the liver removed, glucose loading did not result in normal glucose tolerance, findings which supported their conclusions. Although Soskin's experiments reveal that normal glucose utilization is dependent upon insulin, they do not prove that it is dependent upon the presence of a fixed amount of insulin. Despite the administration of insulin by constant infusion, it is possible that the rate of infusion exceeded the rate of degradation. Therefore, insulin may have been accumulating. Since plasma insulin concentrations were not measured, progressively increasing insulin levels were not excluded. Furthermore, failure to attain normal glucose tolerance in hepatectomized animals with an intact pancreas does not exclude increased insulin secretion as an important factor in obtaining normal glucose tolerance. Soskin's own observations, and those of the present study, indicate that the liver accounts for a significant portion of a glucose load. It seems reasonable that removal of this quantitatively important insulin-responsive organ, even in the presence of increased amounts of insulin, accounted for the impaired glucose tolerance observed by Soskin and co-workers in their hepatectomized dogs. As Park and associates have shown (28), the rate of glucose transport from extracellular fluid into muscle cells is dependent upon extracellular glucose concentration. In the presence of insulin, the rate of glucose transport is increased for any given glucose concentration. It is likely that a significant number of glucose transport sites had been affected by insulin during the prolonged insulin infusion in Soskin and co-workers' studies (27). Under this circumstance, normal glucose disappearance after glucose loading would be expected.

There appears to be considerable evidence to support the view that increased secretion of endogenous insulin, secondary to arterial hyperglycemia, accounts for a decrease in hepatic glucose output and subsequent net hepatic uptake of glucose. It has been demonstrated that insulin is released promptly into pancreatic venous blood after administration of glucose (3, 4). The slow intravenous infusion of insulin produces a prompt fall in hepatic glucose output, even within 10 minutes (1). In the present studies insulin administration prior to glucose loading resulted in a lowering of the arterial glucose concentration at which net hepatic uptake of glucose was observed. The impaired response of the liver to glucose infusion in diabetic dogs is rapidly improved toward normal by insulin administration (26). In the presence of increased insulin secretion, the level of blood sugar probably also determines the extent to which the liver and peripheral tissues dispose of a glucose load. Nevertheless, significant insulin effects on the liver, independent of blood glucose levels, were observed in the present studies. Thus, in Dogs 522, 525 and 610, net hepatic uptake of glucose was as great or greater at a time when the blood glucose concentration was falling, and the arterial glucose level was lower than it was earlier in the study when arterial blood sugar was rising. Indeed, in Dog 119, pretreated with insulin, a positive glucose balance across the liver was observed at arterial glucose concentrations even lower than control. Finally, the persistence of a decreased hepatic glucose output, despite a fall in arterial glucose concentration to values lower than control during the recovery period in four of the dogs in these studies (326, 327, 525, 610), suggests a continuing hepatic action of endogenous insulin, previously secreted during the period of hyperglycemia.

A number of previous investigations has been concerned with the effects of glucose loading on hepatic glucose metabolism. The changes in hepatic glucose balance observed during glucose infusion in our studies in the dog closely resemble the findings of Soskin, Essex, Herrick and Mann (5). Their observations, like our own, are based upon direct measurements of hepatic blood flow and the concentration differences of glucose in blood entering and leaving the liver. Most of their data were obtained in acutely operated dogs given a single rapid intravenous injection of glucose. In only two of their studies was glucose administered by constant intravenous infusion.

Studies in which glucose concentration in arterial, portal and hepatic venous blood was determined, without concomitant measurements of hepatic blood flow, also provide evidence for, but no quantitation of, a decrease in hepatic glucose output and net hepatic glucose uptake during glucose feeding (6) and infusion (7). Bondy, James and Farrar (29), and Myers (23), utilizing hepatic vein catheterization in man, found evidence of glucose retention in the splanchnic viscera after the intravenous administration of glucose. In such studies, however, as Bondy has pointed out, it is impossible to differentiate changes in hepatic glucose metabolism from over-all splanchnic metabolism.

Whereas the above results are in keeping with the findings of the present experiments, studies based on two different isotope dilution techniques are either inconclusive or fail to detect a hepatic response. In the single injection method used by both Searle and Chaikoff (8) and Reichard, Friedmann, Maass and Weinhouse (9), changes in the specific activity of plasma glucose were followed after administration of a tracer dose of glucose-C^{14}. The exponential decline in specific activity during the control period was superseded by a "plateau" after the administration of an unlabeled glucose load. This change in plasma glucose specific activity was attributed to a cessation of hepatic glucose output (8, 9). Berson, Weisenfeld and Pascullo conducted similar experiments in rabbits (10) and have challenged the validity of this interpretation. On theoretical grounds, these authors concluded that "a short period in which the specific activity in the blood remains constant following unlabeled glucose injection is an obligatory consequence of the kinetics of glucose mixing and distribution even if there is no inhibition of glucose production." The studies of Steele, Bishop and Levine (11) also show that the kinetics of mixing of injected glucose may result in a plateauing of glucose specific activity under circumstances in which a decrease in hepatic glucose output could not have occurred. In their studies in eviscerated animals, hepatic glucose output was replaced by a constant infusion of unlabeled glucose. Plateauing of the specific activity of plasma glucose was observed in these animals after administration of a glucose load, even though the constant infusion of glucose was maintained.

To overcome these objections to the single injection technique, the priming dose-constant infusion method of administering glucose-C^{14} has been utilized by Steele and Marks in two experiments (12) and by de Bodo and associates in two experiments (13). No evidence of a decrease in hepatic glucose output after glucose loading was noted in their studies. As was pointed out in a previous publication (1), a major drawback to the isotope dilution studies is that they can measure only new glucose production by the liver. Such techniques cannot measure hepatic glucose utilization or differentiate it from peripheral glucose utilization. The failure of the priming dose-constant infusion studies to detect an alteration in hepatic glucose output after glucose loads, therefore, cannot be considered as unequivocal evidence that such an effect does not occur.

The data accumulated in this and previous studies (1) indicate the presence of a sensitive, integrated system geared to the metabolism of ingested carbohydrate by the liver. The organization of this system appears to be well suited structurally by virtue of the anatomical relationships of the gastrointestinal tract, pancreas, and liver to the portal vein. Thus, glucose absorbed from the intestine passes into portal venous blood where it mixes with insulin released from the pancreas. Glucose and insulin, in concentrations higher than those possible for any other organ, are then carried directly to the liver, a situation which appears to be ideal for the hepatic metabolism of glucose. In the present studies, conducted in dogs with end-to-side portacaval shunts, not only did the insulin secreted in response to the glucose load bypass the liver initially, but the same was true of the glucose that was infused into a peripheral vein. Under these circumstances, the liver was exposed to relatively lower concentrations of both insulin and glucose than would have occurred after the oral ingestion of a carbohydrate load in intact animals. Nevertheless, the total quantity of glucose accounted for by an alteration in hepatic glucose metabolism was appreciable. Indeed, of the glucose which disappeared from the glucose pool, almost as much was accounted for by a change in hepatic glucose metabolism as by an increase in peripheral glucose utilization. Normally, when the liver alone is exposed to the

high concentrations of glucose and insulin present in portal blood after feeding, it would seem reasonable to expect the liver to account for an even greater proportion of a glucose load.

These remarks should not be construed to minimize the importance of the peripheral tissues in the disposition of a carbohydrate load. Previous studies from this laboratory have indicated that the proportion of the secreted insulin which is bound to the liver during the initial transhepatic circulation continually decreases when the intact subject receives carbohydrates (30, 31). The peripheral tissues are thereby supplied with a progressively increasing proportion of the secreted insulin. Indeed, in the present studies with prolongation of the glucose infusion and with larger carbohydrate loads, the peripheral tissues played a proportionately greater role in the disposition of this infused carbohydrate. It should be emphasized that *both* the liver and the peripheral tissues play important roles in carbohydrate utilization. Furthermore, these roles are directly affected by endogenous insulin, which under physiologic conditions is secreted in response to hyperglycemia.

SUMMARY AND CONCLUSIONS

The effect of glucose infusions upon hepatic glucose balance was appraised in dogs with portacaval shunts. This preparation was chosen since it permits determination of changes in hepatic rather than in splanchnic glucose metabolism.

The data indicate that the liver responds to a glucose load first by a decrease in net glucose output, and then by an actual uptake or storage of glucose. These changes occur quickly and are apparently mediated by endogenous insulin which is secreted in response to a rising blood sugar. Quantitatively, these hepatic effects are significant, the liver accounting for almost as much of the infused glucose load as peripheral tissues.

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