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Research Article

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ABSTRACT The effects of glucose on renal bicarbonate reabsorption were investigated in the dog. The infusion of small amounts of glucose calculated to slightly exceed the renal threshold for glucose absorption increased bicarbonate reabsorption in bicarbonate loaded dogs. Galactose in similar doses also increased the reabsorption of filtered bicarbonate. This effect is not due to insulin secretion since insulin alone did not alter bicarbonate reabsorption and the infusion of glucose into alloxan-diabetic dogs given a steady infusion of insulin also enhanced bicarbonate reabsorption. It is more likely that the increased tubular reabsorption of glucose, secondary to an increased filtered load, resulted in the increase in bicarbonate reabsorption since phlorizin reversibly inhibits the effect of glucose.

INTRODUCTION

Mannitol infusion in the dog has been shown to increase the urinary excretion of bicarbonate (1, 2). A similar effect has been shown with urea (2). While not previously investigated in the dog, glucose, another osmotic agent, increases bicarbonate reabsorption in man (3). This may not be a unique effect of glucose since mannitol also increases hydrogen ion secretion in man (4). Unlike mannitol and urea however, which are filtered and then passively reabsorbed to varying degrees, glucose is actively reabsorbed predominantly in the proximal convoluted tubule (5). Moreover, glucose is also metabolized by the kidney (6) and may thereby contribute to energy production and indirectly to the kidney's transport functions. The intriguing possibility exists, therefore, that glucose may differ from other osmotic agents in its effect on renal reabsorption of bicarbonate. Since mannitol decreases bicarbonate reabsorption in the dog, this species seems ideally suited for investigating the possibility that glucose may actually increase bicarbonate reabsorption. The studies herein reported were designed to investigate this problem.

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METHODS

Experiments were performed on mongrel dogs of either sex, weighing between 15 and 30 kg. Animals were anesthetized with intravenous sodium pentobarbitol, 30 mg/kg body wt initially and additional doses given as needed. After induction of anesthesia, the trachea was intubated and respiration supported by a Harvard large-animal respirator (Harvard Apparatus Co., Millis, Mass.). Respiratory rate and tidal volume were adjusted to maintain P_{CO_2} between 35 and 45 mm Hg or close to this range throughout the experiment. Bilateral femoral arterial and venous polyethylene catheters were inserted through inguinal incisions. The ureters were cannulated with PE 100 tubing through a suprapubic midline incision.

After completion of the surgical procedures, the animals were allowed approximately 60 min to stabilize. The infusion of solutions containing sodium [^{125}I]iothalamate, [^{3}H]inulin, or chemically pure inulin for the determination of glomerular filtration rate (GFR) [1] was then begun.

Five major groups of studies were performed:

Group I. In this group, 17 animals were loaded with bicarbonate before the control collections by using a solution containing 150 meq/liter of $NaHCO_3$ and 5 meq/liter K_2CO_3. When the blood bicarbonate had reached at least 30 meq/liter, the experiment was begun. In each experiment, three or four control collections were made each lasting 10–15 min, and the animal was then given glucose in a

[1] *Abbreviations used in this paper:* GFR, glomerular filtration rate; $R_{HCO_3^-}$/GFR, reabsorbed HCO_3^- per unit GFR; RPF, renal plasma flow; $U_{HCO_3^-}V$, HCO_3^- excretion rate; $U_{Na}V$, sodium excretion rate; $U_{P_{CO_2}}$, urine P_{CO_2}; U_{pH}, urine pH.

loading dose of 0.8 g/kg body wt; this was followed by a maintenance solution of 25% glucose in distilled water, given at a rate of 1 ml/min. When the urine became slightly positive for sugar (Clinistix, Ames Co., Elkhart, Ind.), three or four collections 10–15 min each were made during these experimental periods. In 11 of the 17 experiments, the glucose was then discontinued, and when the urine was free of glucose, two or three further collections were made each 10–15 min in duration.

Group II. In this group of eight animals prepared as for the group I above, after the administration of bicarbonate solution and the collection of control periods, the animals were given galactose in a loading dose of 0.4 g/kg body wt followed by a maintenance solution of galastose in distilled water infused at a rate calculated to deliver 10 mg/kg/min. Collections during the experimental period were then made. Galactose infusions were then discontinued, and when the urine became free of reducing substances (Clinitest, Ames Co.), three or four additional collections were made.

Group III. In this group of six animals the effect of systemic insulin was evaluated. After bicarbonate loading, control collections were obtained. Systemic insulin in a loading dose of 1.0 U/kg followed by a maintenance dose of 0.08 U/kg/min in normal saline was given. After approximately 20–30 min of equilibration, four or five additional collections were made.

Group IV. In this group of five animals, diabetes mellitus was experimentally induced by the administration of 50 mg/kg alloxan intravenously 5–7 days before the experiment. Blood sugar levels were determined daily and the experiment performed when it had reached 200–300 mg/100 ml. After the animals were bicarbonate loaded as previously described, several control collections were made. Insulin was then given systemically as described for group III above and several experimental periods obtained. Glucose infusion was then given systemically as for group I while insulin infusion was continued, and additional collections were made.

Group V. Finally, in five animals, the effect of phlorizin was evaluated. The animals were first bicarbonate loaded, and several control periods collected. Glucose was then given in the same manner as described for group I and several more experimental periods were obtained. Phlorizin was then infused intravenously at a rate of 5 μg/kg/min; additional collections followed. Phlorizin was then discontinued and several collections were made during the recovery period. Finally, the glucose infusion was discontinued, and when sugar had disappeared from the urine (Clinistix), several more periods were obtained.

GFR was determined by the clearances of [^{125}I]iothalamate (Glofil, Abbott Laboratories, North Chicago, Ill.), [^{3}H]inulin, or chemically pure inulin. A loading dose of 0.5 μCi/kg followed by a maintenance dose of 0.5 μCi/kg/h was given in experiments utilizing [^{125}I]iothalamate or [^{3}H]inulin. When chemically pure inulin was used the loading dose was 1.5 mg/kg and the maintenance dose 2.5 mg/kg/h. [^{125}I]iothalamate in plasma and urine was measured in a Packard auto-gamma counter (Packard Instrument Co., Inc., Downers Grove, Ill.), and [^{3}H]inulin in a Nuclear-Chicago liquid scintillation counter (Nuclear-Chicago Corp., Des Plaines, Ill.). Inulin was measured in a Technicon Autoanalyzer (Technicon Instruments Corp., Tarrytown, N. Y.).

Glucose determinations were done by the glucose oxidase method using the Boehringer Mannheim blood sugar test set. Protein-free filtrates were made of blood collected in fluoride-containing tubes by using perchloric acid. Urine glucose determinations were done on diluted specimens.

Sodium and potassium determinations were done on an Instrumentation Laboratory, Inc. (Lexington, Mass.) (IL) flame photometer. Samples of blood and urine for pH and P_{CO_2} determination were collected as previously described (2) and measured immediately on an IL pH/P_{CO_2} meter. Bicarbonate values in all but four experiments were calculated from the pH and P_{CO_2} as previously reported (2).

In four experiments, plasma and urine bicarbonate concentrations were determined manometrically by using the Natelson microgasometer. In over 100 samples of plasma and urine in which bicarbonate was simultaneously calculated from the pH and P_{CO_2} and also measured manometrically the mean of the ratios of the calculated to the mea-

TABLE I

An Illustrative Experiment of the Effects of Glucose on Bicarbonate Excretion

Time	Urine flow	GFR	$U_{Na}V$	U_KV	U_{pH}	U_{PCO_2}	$U_{HCO_3^-}V$	Plasma Na	Plasma K	Blood pH	Blood P_{CO_2}	Blood HCO_3^-	$R_{HCO_3^-}$/GFR	C_{Na}/GFR × 100
min	*ml/min*	*ml/min*	*μeq/min*	*μeq/min*		*mm Hg*	*μmol/min*	*meq/liter*	*meq/liter*		*mm Hg*	*meq/liter*	*mmol/liter*	%
−90	B_{pH} = 7.35; B_{PCO_2} = 35.5 mm Hg													
−75	Solution containing 150 meq/liter $NaHCO_3$ and 5 meq/liter K_2CO_3 started at 25 ml/min i.v.; Glofil started, 0.5 μCi/kg loading and 0.5 μCi/kg/h in $NaHCO_3$ solution thereafter.													
0	B_{pH} = 7.53; B_{PCO_2} = 37.0; B_{HCO_3} = 30.9; $NaHCO_3$ solution reduced to 10 ml/min.													
0–10	8.8	69	761	172	7.79	61	689	131.5	2.5	7.53	37.5	31.3	21.2	8.4
10–30	8.1	65	717	142	7.77	66	656	131.0	2.2	7.54	36.5	31.1	21.1	8.4
40	Glucose 0.8 g/kg loading dose; 25% solution at 1 ml/min thereafter.													
50–60	9.1	78	660	100	7.61	63	466	129.0	1.9	7.53	41.0	34.2	28.2	6.5
60–70	9.3	82	609	98	7.60	61	444	126.0	1.9	7.54	45.5	38.8	33.4	5.9
70–80	9.0	94	540	86	7.52	65	376	127.0	1.9	7.51	43.5	34.6	30.6	4.5
80–90	8.8	100	541	92	7.50	67	363	128.5	1.7	7.50	44.0	34.2	30.6	4.2
90	25% Glucose solution discontinued.													
140–150	7.8	57	597	121	7.72	61	507	129.5	2.0	7.56	35.5	31.7	22.8	8.1

$B_{HCO_3^-}$, B_{PCO_2}, and B_{pH}, blood HCO_3^-, P_{CO_2}, and pH, respectively; C_{Na}/GFR × 100, fractional clearance of sodium; $R_{HCO_3^-}$/GFR, reabsorption of bicarbonate per unit GFR; U_KV, potassium excretion rate. Only illustrative periods are shown. In this experiment bicarbonate was calculated from pH and P_{CO_2}.

TABLE II

Effects of Glucose on Bicarbonate Reabsorption—Electrode Method

	GFR			$U_{Na}V$			$U_{HCO_3^-}V$			Plasma HCO_3^-			$C_{Na}/GFR \times 100$			$R_{HCO_3^-}/GFR$		
	C	Gl	R	C	Gl	R	C	Gl	R	C	Gl	R	C	Gl	R	C	Gl	R
	ml/min			*μeq/min*			*μmol/min*			*meq/liter*			%			*mmol/liter*		
1	64	63		479	309		400	200		33.1	33.9		5.1	3.6		26.9	30.6	
2	46	50		936	980		996	1,004		51.5	54.2		14.3	14.1		29.9	34.1	
3	21	26		510	528		599	584		55.9	59.6		16.9	15.7		27.6	36.6	
4	62	72		1,572	1,562		1,506	1,403		53.6	53.6		17.7	15.7		29.1	33.4	
5	96	125		1,508	1,166		1,119	929		39.9	40.3		11.0	6.6		27.9	32.9	
6	31	37		887	938		742	771		50.5	48.6		23.6	20.8		26.4	28.6	
Mean	53	62		982	914		894	815		47.4	48.4		14.8	12.8		28.0	32.7	
SD	26.9	35.0		472	440		397	440		8.9	9.6		6.3	6.4		1.3	2.8	
P		>0.05			>0.3			>0.1			>0.2			<0.02			<0.005	
7	58	66	56	1,087	1,213	1,208	950	938	1,014	38.7	37.9	42.4	12.8	12.8	14.8	22.2	23.6	24.3
8	51	53	46	1,205	1,180	1,071	903	844	792	34.5	36.0	35.0	16.5	16.2	16.8	16.9	20.1	17.5
9	71	88	58	737	586	589	656	412	493	31.3	35.5	33.6	8.0	5.3	7.9	22.0	30.7	25.0
10	63	68	58	1,052	918	929	976	817	822	38.6	38.3	39.4	12.0	10.1	11.8	23.2	26.0	25.0
11	63	65	54	1,173	791	765	968	714	681	32.8	33.7	32.2	12.7	9.1	9.8	17.4	27.0	19.5
12	44	50	37	1,674	1,382	390	1,465	1,036	399	48.3	44.1	32.6	24.9	19.7	7.4	15.3	23.2	21.9
13	60	76	64	881	1,120	1,200	783	842	1,013	32.5	34.1	39.3	10.2	10.5	13.4	19.4	23.0	23.3
Mean	59	67	53	1,116	1,027	878	957	800	745	41.6	42.3	36.4	13.9	12.0	11.7	19.5	24.8	22.4
SD	8.8	13.0	9.0	296	275	313	252	199	238	9.0	8.9	4.0	5.5	4.8	3.5	3.1	3.4	2.9
P		<0.01	<0.05		>0.05	>0.05		>0.05	>0.05		>0.05	>0.05		>0.05	>0.05		<0.005	<0.025

For meaning of symbols refer to Table I. C, Gl, and R represent the periods during control, glucose infusion, and recovery, respectively. The *P* values are for the differences between paired values in the respective column and the control column.

sured values for plasma was 0.996±0.04 and for urine was 0.932±0.07; neither value is significantly different from unity ($P > 0.1$). Paired data were analyzed by the paired *t* test method; all other data were analyzed by Dunnett's test for the analysis of variance (7).

RESULTS

Effects of glucose loads. The effects of glucose on bicarbonate reabsorption in a bicarbonate-loaded dog are illustrated in Table I and the means of all the data are summarized in Tables II and III. In the illustrative experiment (Table I) the infusion of glucose raised the GFR; plasma [HCO_3^-] also rose. Despite the rise in filtered HCO_3^-, urine pH and excreted HCO_3^- fell, as did the excretion and fractional clearance of sodium. Reabsorbed HCO_3^-, therefore, rose. These changes reverted towards control after discontinuation of glucose infusion. In Table II the data are divided into two groups, depending on whether recovery periods were collected; in both subgroups bicarbonate was calculated from pH and P_{CO_2}. In both groups GFR rose during glucose infusion (although significantly only in the second group), and fell significantly in the recovery period in the second group. The serum sodium fell slightly but significantly in both groups. Blood [HCO_3^-] did not change significantly. Despite the rise in filtered HCO_3^- in many experiments (because of raised GFR) the excretion of HCO_3^- fell in 10 of the 13 experiments (although the changes are not statistically different in

TABLE III

Effects of Glucose on Bicarbonate Reabsorption—Manometric Method

	GFR			$U_{Na}V$			$U_{HCO_3^-}V$			Plasma HCO_3^-			$C_{Na}/GFR \times 100$			$R_{HCO_3^-}/GFR$		
	C	Gl	R	C	Gl	R	C	Gl	R	C	Gl	R	C	Gl	R	C	Gl	R
	ml/min			*μeq/min*			*μmol/min*			*meq/liter*			%			*mmol/liter*		
1	59	63	59	426	352	235	526	308	313	35.4	36.9	35.3	5.1	4.1	2.8	27.0	32.1	29.8
2	51	36	26	301	121	147	264	87	158	30.8	32.3	32.9	4.2	2.4	4.1	25.6	29.9	26.8
3	44	53	30	402	362	226	370	244	230	34.9	33.9	32.6	6.3	4.8	5.2	26.3	29.3	24.9
4	67	75	59	353	205	182	369	193	205	33.4	33.6	34.0	3.6	2.0	2.2	27.8	31.0	30.0
Mean	55	57	44	371	260	198	383	208	227	33.6	34.2	33.7	4.8	3.3	3.6	26.7	30.6	27.9
SD	9.9	16.5	18.0	55	117	41	108	93	65	2.1	1.9	1.2	1.2	1.3	1.3	0.9	1.2	2.5
P		>0.05	>0.05		<0.005	<0.005		<0.005	<0.005		>0.05	>0.05		<0.025	<0.05		<0.005	<0.005

For meaning of symbols refer to Tables I and II.

the two groups). Consequently, reabsorbed HCO_3^- ($R_{HCO_3^-}$/GFR) rose significantly in both groups (28.0 to 32.7 and 19.5 to 24.8, $P < 0.005$); $R_{HCO_3^-}$/GFR fell after the discontinuation of glucose although it remained above control. The increase in HCO_3^- absorption was not associated with any significant changes in urine pH (U_{pH}) or P_{CO_2} (U_{PCO_2}) nor in the excretion and fractional clearance of sodium. Blood P_{CO_2} rose slightly from 41 to 44 mm Hg but this change is not sufficient to account for the increase in reabsorbed HCO_3^-, nor is the slight but significant drop in serum potassium ($\Delta = -0.4$ meq/liter in both groups). Qualitatively similar results were observed in the four dogs in which bicarbonate in plasma and urine was measured manometrically. Glucose raised GFR insignificantly but produced a significant drop in urine sodium and urine bicarbonate excretion and in fractional sodium excretion and a significant rise in $R_{HCO_3^-}$/GFR (Table III).

Effects of galactose loads. Table IV shows the means of observations in each of eight experiments in which galactose was infused in bicarbonate-loaded dogs. Galactose infusion did not alter GFR, sodium excretion rate ($U_{Na}V$), HCO_3^- excretion rate ($U_{HCO_3^-}V$), or fractional clearance of sodium significantly; urine pH fell significantly as did the serum sodium and potassium. Reabsorbed bicarbonate, however, rose significantly from a mean of 23.9 mmol/liter in control periods to a mean of 27.9 mmol/liter after galactose administration; it fell to a mean of 23.0 during recovery periods, a value which is not significantly different from control. Blood P_{CO_2} did not change significantly and the drop in serum potassium was small ($\Delta = -0.3$ meq/liter) and could not account for the change in $R_{HCO_3^-}$.

Effects of insulin. Table V lists the means of observations in each of six experiments in which the effect of systemic insulin infusion was investigated in bicarbonate-loaded dogs. GFR, $U_{Na}V$, U_{pH}, and $U_{HCO_3^-}V$ were unchanged. Fractional clearance of sodium rose from 10.5 to 12.5%, a change which was significant. Reabsorbed bicarbonate, however, changed randomly and insignificantly even though the serum potassium fell significantly ($\Delta = -0.6$ meq/liter). The change in plasma glucose from a mean of 116 mg/100 ml to 46 mg/100 ml was highly significant.

Studies in diabetic animals. Table VI summarizes the results of five experiments in dogs with alloxan diabetes. GFR was not significantly affected by the systemic infusion of insulin or the addition of glucose. Sodium excretion, bicarbonate excretion, U_{pH}, and U_{PCO_2} were also unchanged. Reabsorbed bicarbonate during insulin infusion remained unchanged from control periods even though serum potassium fell significantly ($\Delta = -0.8$ meq/liter); it rose significantly when glucose was superimposed on insulin infusion while serum potassium did not change further. Plasma glucose fell from a mean of 250 mg/100 ml to a mean of 77 mg/100 ml after insulin and returned to 239 mg/100 ml after glucose infusion. These changes were highly significant.

Effects of phlorizin. The results of five experiments during phlorizin infusion into bicarbonate-loaded dogs receiving glucose are shown in Table VII.

GFR fell significantly after the infusion of phlorizin and remained reduced after phlorizin had been stopped. There were no significant changes in U_{pH}, U_{PCO_2}, bicarbonate, or sodium excretion. Reabsorbed bicarbonate, on the other hand, rose significantly from a mean of 25.8 mmol/liter during control periods to a mean of 29.8 mmol/liter during glucose infusion. During phlorizin infusion, it fell to 28.0 mmol/liter, a value which is not significantly different from control. When phlorizin was discontinued, bicarbonate reabsorption rose significantly to a mean of 30.1 mmol/liter. During re-

TABLE IV

Effects of Galactose on Bicarbonate Reabsorption

Experiment no.	GFR			$U_{Na}V$			$U_{HCO_3^-}V$			Plasma HCO_3^-			C_{Na}/GFR × 100			$R_{HCO_3^-}$/GFR		
	C	Ga	R	C	Ga	R	C	Ga	R	C	Ga	R	C	Ga	R	C	Ga	R
	ml/min			*μeq/min*			*μmol/min*			*meq/liter*			%			*mmol/liter*		
1	30	31	21	369	345	386	381	389	369	36.7	40.6	41.7	7.2	7.9	12.8	26.2	28.3	24.2
2	50	55	58	746	864	1,076	680	796	998	38.0	40.5	37.0	10.2	10.9	13.2	24.4	26.0	19.6
3	22	18	16	469	336	416	560	422	643	46.1	52.4	49.9	13.9	12.7	19.2	20.9	28.8	10.3
4	24	27	28	603	440	382	544	423	377	42.7	39.7	38.5	17.6	11.4	9.7	19.6	24.1	24.8
5	60	50	59	636	561	613	566	497	568	37.4	40.1	37.9	7.3	8.2	7.4	28.0	30.2	28.2
6	39	40	34	409	431	652	298	357	592	35.5	39.1	39.1	7.1	7.3	12.7	27.3	30.1	21.7
7	42	44	32	831	451	569	687	360	507	37.2	36.9	44.3	13.8	7.2	12.7	20.6	28.7	28.5
8	49	48	44	414	547	748	404	527	654	32.4	37.8	41.3	5.9	8.0	11.6	24.0	26.7	26.6
Mean	40	39	37	560	496	605	515	459	589	38	41	41	10.4	9.2	12.4	23.9	27.9	23.0
SD	13.0	12.7	16.0	171	170	233	141	146	198	4.3	4.8	4.2	4.3	2.1	3.4	3.2	2.1	6.0
P		>0.05	>0.05		>0.05	>0.05		>0.05	>0.05		>0.05	>0.05		>0.05	>0.05		<0.05	>0.05

Ga, periods during galactose infusion. For meaning of other symbols refer to Tables I and II.

TABLE V

Effects of Insulin on HCO_3^- Reabsorption

Experiment no.	GFR		$U_{Na}V$		$U_{HCO_3^-}V$		Plasma HCO_3^-		Plasma Glucose		$C_{Na}/GFR \times 100$		$R_{HCO_3^-}/GFR$	
	C	I	C	I	C	I	C	I	C	I	C	I	C	I
	ml/min		*μeq/min*		*μmol/min*		*meq/liter*		*mg/100 ml*		%		*mmol/liter*	
1	60	64	1,016	1,309	1,044	1,207	37.5	41.0	92	26	11.3	13.4	20.2	22.1
2	26	27	542	650	670	705	34.0	32.3	122	68	14.5	17.0	8.0	6.0
3	53	47	645	525	745	581	34.1	32.9	117	52	7.9	7.3	19.9	20.3
4	45	34	746	772	805	788	36.8	36.7	121	38	11.2	15.4	18.8	13.1
5	52	47	695	695	752	736	43.3	43.8	130	55	8.8	9.4	28.8	28.2
6	69	61	802	943	837	842	32.5	31.7	115	38	9.4	12.6	20.4	17.7
Mean	51	47	741	816	809	810	36.4	36.4	116	46	10.5	12.5	19.4	18.0
SD	6.0	5.9	66	114	53	87	3.9	5.0	5.3	6.1	1.0	1.5	2.7	3.1
P		>0.05		>0.05		>0.05		>0.05		<0.005		<0.025		>0.05

I = periods during insulin infusion. For meaning of other symbols refer to Tables I and II.

covery periods, when both phlorizin and glucose were discontinued bicarbonate reabsorption fell to a mean of 27.9 mmol/liter, a value not significantly different from control. The serum potassium fell by 0.5 meq/liter after glucose infusion but did not change further during the rest of the experiment. Thus, the changes in serum potassium did not correlate with the changes in $R_{HCO_3^-}$. Blood P_{CO_2} rose slightly during glucose infusion. Plasma glucose reflected the experimental maneuvers. It rose from a mean of 110 mg/100 ml to a mean of 214 mg/100 ml after glucose infusion and fell to a mean of 181 mg/100 ml when phlorizin was given but remained at about this level when it was discontinued. Glucose in plasma fell to a value not different from control when its infusion was stopped.

DISCUSSION

The results of the present study demonstrate that intravenous doses of glucose, which produce blood levels only slightly in excess of the renal threshold, produced a consistent increase in bicarbonate reabsorption and this effect was reversed in most experiments when glucose administration was stopped and the glucosuria was allowed to subside. This enhancement of bicarbonate reabsorption assumes added significance when it is considered that the continued infusion of bicarbonate alone has been reported to reduce bicarbonate reabsorption (8). The effect of glucose on bicarbonate reabsorption does not appear to be unique to this compound since galactose, another hexose that is reabsorbed and metabolized by the kidney, similarly increased bicarbonate reabsorption when given in equimolar doses.

Several possibilities may be suggested to explain the glucose-induced increase in bicarbonate reabsorption. Alterations in renal hemodynamics have been shown to alter bicarbonate reabsorption (9, 10) and it is possible that the effect of glucose may have been hemodynamically induced. As previously shown in man (11) glucose infusion increased GFR in the dog. This could not account for the increase in bicarbonate reabsorption, however, since the increase in GFR was not consistent (as seen in Tables II, III, VI, and VII). In addition, galactose, which also increased bicarbonate reabsorption, did not significantly alter GFR. Although renal plasma flow (RPF) was not measured in the present study it has been shown to increase after glucose infusion (12). Increase in RPF induced by vasodilator agents, however, has been shown to decrease rather than increase bicarbonate reabsorption (10). Thus, it seems unlikely that hemodynamic changes exerted a primary influence in the changes observed.

An alternative explanation may be that glucose stimulates insulin secretion which in turn may enhance bicarbonate reabsorption. Insulin has been shown to be antidiuretic and antinatriuretic (13–16), and it is possible that it may secondarily increase hydrogen ion secretion in exchange for sodium reabsorption. This does not seem likely, however, since the administration of insulin to bicarbonate-loaded dogs did not reduce sodium excretion and produced instead a small but insignificant decrease in bicarbonate reabsorption. Insulin also failed to alter bicarbonate reabsorption in alloxan-diabetic dogs. It is possible, however, that insulin does enhance $R_{HCO_3^-}$ but that its effect is nullified by the drop in blood and filtered glucose which decreases $R_{HCO_3^-}$. Secretion of insulin, however, cannot alone explain the effect of glucose since the administration of glucose to alloxan-diabetic dogs which are incapable of secreting insulin resulted in the predicted increase in $R_{HCO_3^-}$.

Other factors which could have effected the increase in bicarbonate reabsorption are the decrease in serum potassium and the increase in blood P_{CO_2} and plasma $[HCO_3^-]$. The drop in serum potassium could not have

TABLE V

Effects of Insulin Alone and wi

	GFR			$U_{Na}V$			$U_{HCO_3}V$			Plasm HCO_3^-		
	C	I	I + Gl	C	I	I + Gl	C	I	I + Gl	C	I	I + G
		ml/min			*μeq/min*			*μmol/min*			*meq/liter*	
1	20	18	38	467	416	340	412	370	216	33.0	33.3	36.5
2	30	25	27	299	332	426	315	313	412	42.7	41.3	48.0
3	58	35	45	640	309	565	556	370	605	33.5	31.1	38.2
4	43	36	33	824	800	831	527	562	638	31.1	36.7	39.4
5	32	31	30	821	624	669	747	577	515	37.1	35.8	40.2
Mean	36	29	35	611	496	566	511	438	477	35.5	35.6	40.5
SD	6.5	3.4	3.2	102	94	87	73	55	76	4.6	3.9	4.4
P		>0.05	>0.05		>0.05	>0.05		>0.05	>0.05		>0.05	<0.00

For meaning of symbols refer to Tables I and II.

contributed to the increase in R_{HCO_3} because the changes were small and persisted after glucose was discontinued (Table II) or after phlorizin (Table VII) even though R_{HCO_3} had fallen. Insulin also reduced serum potassium without any effect on R_{HCO_3} (Tables V and VI). The changes in P_{CO_2} were also too small to account for the changes in R_{HCO_3} observed. Increase in filtered HCO_3^- does not appear to have caused the increase in R_{HCO_3} either, since in many experiments bicarbonate excretion actually fell and the urine became more acid (Tables I and II). Furthermore, blood $[HCO_3^-]$ was not increased in all experiments (Tables II, III, IV, and VII). Where it rose, the rise must have been largely the consequence of increased HCO_3^- reabsorption rather than its cause.

An increase in glucose reabsorption secondary to the increased filtered load may have led to the increase in bicarbonate reabsorption. To examine this possibility dogs were given phlorizin after the enhancing effect of glucose on bicarbonate reabsorption had occurred. Phlorizin consistently decreased bicarbonate reabsorption in all dogs and its discontinuation resulted in the return of bicarbonate reabsorption to higher levels. This reversible inhibition by phlorizin of the effect of glucose on bicarbonate strongly suggests that the enhancement of bicarbonate reabsorption is related somehow to the active reabsorption of glucose. The failure of R_{HCO_3} to fall when plasma glucose was reduced by insulin may be due to a counteracting effect of insulin itself. On the other hand, the effect of glucose does not have to be symmetrical; R_{HCO_3} may be set and does not fall when glucose is reduced, but rises when glucose absorption is raised.

It is possible that glucose administration, which results in pyruvate and lactate production (17), may have produced an intracellular acidosis which in turn increased hydrogen ion secretion and bicarbonate reabsorption. Phlorizin could have mitigated the effect of

TABLE VI

Effects of Phlorizin in Bicarbonat

	GFR					$U_{Na}V$					$U_{HCO_3}V$					Plasm HCO	
	C	Gl	Gl + P	Gl	R	C	Gl	Gl + P	Gl	R	C	Gl	Gl + P	Gl	R	C	Gl
			ml/min					*μeq/min*					*μmol/min*			*meq/lit*	
1	67	79	67	70	63	775	613	625	586	653	875	736	629	667	707	36.1	35.(
2	53	49	43	44	45	872	958	936	1,037	1,132	839	853	898	961	1,045	43.1	45.1
3	79	75	64	63	78	1,148	1,176	1,178	1,284	1,438	1,107	995	1,300	1,259	1,355	40.0	42.5
4	43	38	32	37	32	503	348	309	371	443	508	342	370	367	426	39.3	39.(
5	47	38	37	37	45	496	393	356	389	441	426	275	287	330	339	34.5	43.1
Mean	58	56	49	50	53	759	698	681	733	821	751	640	697	717	774	38.6	41.1
SD	15.0	19.9	15.9	15.4	17.9	273	360	374	408	445	280	317	413	396	426	3.4	3.9
P		>0.05	<0.01	<0.025	>0.05		>0.05	>0.05	>0.05	>0.05		>0.05	>0.05	>0.05	>0.05		>0.(

P, periods during phlorizin infusion. For meanings of other symbols refer to Tables I and II.

Glucose in Alloxan-Diabetic Dogs

Plasma Glucose			$C_{Na}/GFR \times 100$			$R_{HCO_3^-}/GFR$		
C	I	I + Gl	C	I	I + Gl	C	I	I + Gl
	mg/100 ml			%			*mmol/liter*	
279	45	282	16.0	15.9	6.4	12.3	13.1	30.7
241	137	289	7.1	9.3	10.9	32.1	28.6	32.9
307	102	276	7.5	5.9	8.5	23.9	20.3	25.1
180	69	182	14.4	15.9	18.3	18.6	21.5	23.0
245	34	169	17.6	14.8	15.2	13.2	17.4	22.7
250	77	239	12.5	12.4	11.9	20.0	20.2	26.9
21.3	18.9	26.3	2.2	2.0	2.2	3.7	2.6	2.0
	<0.005	>0.05		>0.05	>0.05		>0.05	<0.05

glucose by preventing its entry into the tubular cell. This does not seem likely since the administration of phlorizin would not be expected to prevent glucose from gaining access to the proximal tubular cells. In the studies of Tune and Burg (18) the contraluminal border of the proximal tubular cells was found to be more permeable to glucose than was the luminal membrane and glucose could have entered the cell from the blood. Furthermore, the administration of glucose does not increase cortical tissue lactate concentration nor does the administration of phlorizin reduce it (19). It is unlikely, therefore, that glucose may exert its effect by increasing intracellular hydrogen ion concentration. It appears more likely that glucose exerts its effect either directly on bicarbonate reabsorption or indirectly through sodium reabsorption.

A relationship between glucose and sodium reabsorption in the kidney has been known for some time. The administration of glucose to fasting man reduces sodium excretion (20–25) even when the fasting is of short duration (23). An interrelationship between sodium absorption and absorption of glucose has also been shown in clearance experiments (26, 27), in the isolated perfused kidney (28, 29), and in micropuncture experiments (30). It is possible therefore that the changes in bicarbonate reabsorption observed in the present experiments may have been secondary to changes in sodium reabsorption. Changes in sodium excretion, however, were inconsistent in the present experiments. It is possible, on the other hand that at these high rates of $U_{Na}V$ small changes may have been obscured. Alternatively, glucose may have increased proximal tubular reabsorption where the reabsorption of bicarbonate may be the primary event. In a series of studies by Kokko, Rector, and Seldin it was reported that the reabsorption of NaCl from the isolated perfused proximal convoluted tubule was almost entirely dependent on the reabsorption of $NaHCO_3$ (31). In

Loaded Dogs Given Glucose

Plasma HCO_3^-			Glucose					$C_{Na}/GFR \times 100$					$R_{HCO_3^-}/GFR$				
Gl + P	Gl	R	C	Gl	Gl + P	Gl	R	C	Gl	Gl + P	Gl	R	C	Gl	Gl + P	Gl	R
meq/liter					*mg/100 ml*					%					*mmol/liter*		
33.1	38.8	38.0						5.6	4.5	4.6	4.3	4.7	23.0	25.6	23.8	29.2	26.8
45.9	48.9	48.0	116	147	149	156	81	11.3	13.4	14.8	16.4	17.7	27.1	27.9	25.3	27.2	24.7
48.1	48.3	45.7	125	182	165	164	122	9.8	10.5	12.0	13.4	12.1	26.0	29.3	27.9	28.2	28.3
40.4	44.0	41.6	108	263	184	196	75	7.9	6.2	6.4	6.8	9.3	27.3	30.4	28.8	33.9	28.3
42.0	40.6	38.8	89	265	227	216	76	6.9	7.1	6.5	7.2	6.9	25.5	35.8	34.2	31.8	31.2
41.9	44.1	42.4	110	214	181	183	89	8.3	8.3	8.9	9.6	10.1	25.8	29.8	28.0	30.1	27.9
5.8	4.5	4.3	15.3	59.2	33.7	28.0	22.5	2.3	3.6	4.3	5.1	5.0	1.7	3.8	4.0	2.8	2.4
>0.05	<0.005	<0.05		<0.005	<0.025	<0.01	>0.05		>0.05	>0.05	>0.05	>0.05		<0.025	>0.05	<0.01	>0.05

another series of studies, Kokko reported that the omission of glucose from the perfusate of such isolated tubules resulted in a less negative potential difference in the tubular lumen (32). It is conceivable that increasing glucose absorption could increase the negativity of the luminal potential. This could facilitate the absorption of an anion such as HCO_3^-. It is also possible that glucose absorption creates a local concentration gradient for other solutes in the tubular fluid because of the water it obligates. Thus increased glucose absorption could create favorable electrochemical gradients for the movement of HCO_3^- across the luminal membrane of the tubular cells.

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