Relationship of Sodium Reabsorption and Glomerular Filtration Rate to Renal Glucose Reabsorption

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ABSTRACT Glucose reabsorption was measured in dogs in which sodium reabsorption was stimulated by obstruction of the thoracic inferior vena cava or inhibited by volume expansion with Ringer's lactate. Glucose reabsorption was much higher during periods of enhanced sodium reabsorption than during sodium diuresis. The relationship of glucose reabsorption to glomerular filtration rate was examined using data from animals that had fractional sodium excretion rates of less than 1%. Under this condition the relationship of glucose reabsorption to glomerular filtration rate is highly linear. When points obtained during sodium diuresis ($C_{Na}/GFR > 0.1$) are plotted on the same graph, glucose reabsorption at any given glomerular filtration rate is much less than during antidiuresis. Glucose reabsorption divided by glomerular filtration rate varies inversely with fractional sodium excretion. This study demonstrates that glomerular tubular balance for glucose exists in the dog and that this balance is changed when sodium reabsorption changes.

INTRODUCTION

Since the classic experiments of Shannon and coworkers (1, 2) it has been thought that the renal tubules reabsorb all the filtered glucose presented to them until the filtered load of glucose exceeds the maximum reabsorptive capacity of the tubule (Tm_G)[1]; filtered glucose in excess of this maximum reabsorptive capacity escapes reabsorption and appears in the urine.

Recently, the concept of tubular maximum for bicarbonate (3–5) and phosphate has undergone considerable expansion (6–9). It has been clearly demonstrated that the renal reabsorption of these substances is not an independent process regulated only by factors specific to bicarbonate and phosphate, but that the stimulus to renal tubular sodium reabsorption also exerts great influence on bicarbonate and phosphate reabsorption. When sodium reabsorption is enhanced so is that of bicarbonate and phosphate; when sodium reabsorption is diminished the same is true for bicarbonate and phosphate.

Recent studies of glucose reabsorption in the rat (10, 11) have suggested that glucose reabsorption is more complex than originally proposed by Shannon and coworkers. These studies have demonstrated that glucose reabsorption is influenced by both changes in glomerular filtration rate (10) and the reabsorptive rate of sodium (11).

The current study was designed to reevaluate renal glucose reabsorption in the dog, the animal studied by Shannon and coworkers, to determine if glomerular filtration rate and sodium reabsorption were regulators of renal glucose reabsorption in addition to the intrinsic reabsorptive capacity of the tubule for glucose.

METHODS

31 experiments were performed on 26 mongrel dogs.[2] After preparation, the details of which are described below, the animals were anesthetized with sodium pentobarbital. An endotracheal tube fitted with an inflatable cuff was placed in the trachea and connected to a Bird respirator (Phipps & Bird, Inc., Richmond, Va.). 5% dextrose in H_2O containing iothalamate-125 was administered at 1 ml/min throughout each experiment. All clearance periods were 10 min in duration.

20% dextrose in H_2O was infused at varying rates to produce the desired plasma glucose concentration. When-

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[1] *Abbreviations used in this paper:* F_G, filtered glucose; GFR, glomerular filtration rate; T_G, glucose reabsorption; TIVC, thoracic inferior vena cava; Tm_G, maximum reabsorptive capacity of the tubule for glucose.

[2] In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences, National Research Council.

ever the rate of glucose infusion was changed, a 30 min equilibration period was allowed to elapse before another clearance period was begun. All clearance periods were obtained when the plasma glucose concentration was in excess of the renal threshold for glucose. 10–25 clearance periods were obtained from each dog.

Glucose reabsorption was measured in 10 dogs who had received a regular kennel diet (estimated to contain 30 mEq/day of NaCl) to which 85 mEq/day of NaCl had been added for 4 days. In addition, these animals received Ringer's lactate intravenously throughout each experiment at rates of from 1 to 10 ml/min in order to increase urinary sodium excretion.

Glucose reabsorption was measured in 11 dogs who were subjected to acute partial obstruction of the thoracic inferior vena cava (TIVC), sufficient to raise the venous pressure below the obstruction 60–100 mm of H_2O, in order to enhance sodium reabsorption. These dogs received a single dose of 20 mg of furosemide intravenously 72 hr before study during which time they received a salt-free diet. Five of these dogs were restudied without caval obstruction 4–10 days later.

Glucose reabsorption was measured in another group of five dogs who were subjected to acute partial obstruction of the TIVC. When these measurements were completed, the obstruction was removed and Ringer's lactate infused at 10–15 ml/min whereupon an additional series of measurements were made. These animals received the regular kennel diet before study.

In all experiments in which the cava was obstructed, such obstruction was performed at least 90 min before the beginning of the first clearance period.

Arterial blood was obtained via an arterial catheter. Urine was obtained from an indwelling bladder catheter. Glucose concentration in arterial plasma and urine was measured immediately after collection by a glucose oxidase technique using the Beckman glucose analyzer (Beckman Instruments, Inc, Palo Alto, Calif.) This technique was found to be continuously reproducible within an error of less than 2%. All samples were run in triplicate with the mean value used.

Blood CO_2 tension was continuously monitored throughout each experiment and kept in the range of 35–45 mm Hg by appropriate manipulation of the respirator. The techniques used to measure arterial CO_2 tension, plasma, and urine sodium concentration, and iothalamate clearance have been previously described (4). The clearance of iothalamate-125 was considered to equal the glomerular filtration rate (GFR).

RESULTS

The effect of increasing sodium excretion upon glucose reabsorption is illustrated in Table I. In this experiment, glucose reabsorption (T_G) was about 80 mg/min during caval obstruction. When the obstruction was removed, more glucose infused, and sodium diuresis produced by infusing Ringer's lactate, glucose reabsorption fell to about 40 mg/min. This fall was accompanied by an increase in filtered glucose (F_G), an increase in GFR, an almost 30-fold increase in fractional sodium excretion, a 50-fold increase in absolute sodium excretion, and a threefold fall in the ratio of glucose reabsorption to GFR (T_G/GFR). Thus, an increase in fractional and absolute sodium excretion was associated with a fall in absolute glucose reabsorption as well as a fall in glucose reabsorption factored by GFR.

TABLE I

Effect of Caval Obstruction on Glucose Reabsorption

Time	Plasma glucose	Flow	Glucose			GFR	T_G/GFR	C_{Na}/GFR × 100	$U_{Na}V$
			Filtered	Excreted	Reabsorbed				
min	*mg/100 ml*	*ml/min*		*mg/min*		*ml/min*	*mg/ml*	%	*μEq/min*
Dog 12; wt 13.6 kg									
Partially obstruct TIVC; infuse 20% dextrose in H_2O at 1 ml/min									
0– 95									
95–105	405	0.75	137.7	38.5	99.2	34.0	2.9	0.9	43
105–115	392	0.80	130.9	50.1	80.8	33.4	2.4	0.7	35
115–125	408	0.80	139.9	59.8	80.1	34.3	2.3	0.6	28
125–135	395	0.95	141.4	63.0	78.4	35.8	2.2	0.9	46
135–145	436	1.05	153.9	74.0	79.9	35.3	2.3	1.0	50
145–155	410	1.20	163.6	85.5	78.1	39.9	2.0	1.0	61
155–165	443	1.10	169.7	81.4	88.3	38.3	2.3	1.0	52
165–175	444	1.10	170.1	81.5	88.6	38.3	2.3	1.0	52
Remove TIVC obstruction; infuse 20% dextrose in H_2O at 2 ml/min; infuse Ringer's lactate at 15 ml/min									
235–245	516	21.4	300.8	249.5	51.3	58.3	0.9	19.4	1541
245–255	523	22.1	301.2	248.8	52.4	57.6	0.9	20.7	1635
255–265	557	23.8	333.6	275.4	58.2	59.9	1.0	22.5	1856
265–275	561	25.4	338.3	292.9	45.4	60.3	0.8	25.3	2108
275–285	570	26.4	340.9	301.5	39.4	59.8	0.7	27.8	2297

TABLE II

Effect of Progressive Increase in Sodium Excretion on Glucose Reabsorption

Time	Plasma glucose	Flow	Glucose			GFR	T_G/GFR	C_{Na}/GFR × 100	$U_{Na}V$
			Filtered	Excreted	Reabsorbed				
min	*mg/100 ml*	*ml/min*		*mg/min*		*ml/min*	*mg/ml*	*%*	*μEq/min*
Dog 21B; wt 9.4 kg									
Infuse 20% dextrose in H_2O at 0.5 ml/min; Ringer's lactate at 1.5 ml/min									
0–100									
100–110	302	0.55	110.5	26.8	83.7	36.6	2.3	1.3	65
110–120	307	0.60	122.2	30.9	91.3	39.8	2.3	0.9	53
120–130	299	0.95	117.5	33.2	84.3	39.3	2.1	1.8	100
130–140	290	1.35	105.6	28.6	77.0	36.4	2.1	1.3	104
140–150	284	2.15	96.6	24.4	72.2	34.0	2.1	0.8	68
Increase 20% dextrose in H_2O infusion to 1.2 ml/min									
180–190	337	3.0	124.0	44.6	79.4	36.8	2.2	3.1	162
190–200	348	3.5	128.4	57.1	71.3	36.9	1.9	3.2	165
200–210	338	3.8	115.6	54.7	60.9	34.2	1.8	4.3	209
210–220	344	6.6	135.5	67.3	68.2	39.4	1.7	5.5	310
220–230	371	8.9	146.2	90.8	55.4	39.4	1.4	8.9	490
Increase 20% dextrose in H_2O infusion to 2.5 ml/min									
260–270	904	10.3	280.2	244.8	35.4	31.0	1.1	15.3	639
270–280	990	10.7	325.7	293.9	31.8	32.9	1.0	16.2	727
280–290	994	10.0	289.3	265.7	23.6	29.1	0.8	18.4	730
290–300	986	8.2	243.5	216.5	27.0	24.7	1.1	19.1	640

Table II illustrates the effect of steadily increasing the rate of glucose infusion to a dog without caval obstruction. Fractional sodium excretion which was about 1% at the beginning of the study rose to 19%, absolute sodium excretion rose from 68 to 640 μEq/min. Absolute glucose reabsorption which had been greater than 70 mg/min fell to less than 30 mg/min despite a rising filtered load of glucose. The GFR fell when the blood sugar was raised over 900 mg/100 ml—a phenomenon that has previously been described (12). Despite this fall in GFR, T_G/GFR fell by about 50%.

Table III summarizes the results obtained from all the dogs studied. The values reported for the animals subjected to caval obstruction are those obtained when the filtered load of glucose was at its highest. The values reported for the dogs not subjected to caval obstruction are those associated with the highest fractional sodium excretion. For those animals studied both with and without caval obstruction the letter "*a*" represents the values during caval obstruction, while those labeled "*b*" are those obtained without caval obstruction. Dogs 11, 12, 13, 16, and 17 had both studies performed in succession on the same day. Dogs 21–25 were studied on separate days. The weights listed in Table III are the animals' weights before any manipulation of their diet.

As is apparent from Table III, both absolute glucose reabsorption and T_G/GFR are much higher in the animals with caval obstruction (those dogs with [C_{Na}/GFR] × 100 = to 1% or less) than in those animals without caval obstruction ([C_{Na}/GFR] × 100 > 13%). This is best appreciated by comparing F_G, T_G, and T_G/GFR in those animals studied both with and without caval obstruction. Mean F_G was 207 mg/min ±60 (SD) during caval obstruction, without caval obstruction F_G was 243 mg/min ±86 ($P > 0.1$). Mean T_G with caval obstruction was 105 mg/min ±35, without caval obstruction in the same animals T_G was 45 mg/min ±21 ($P < 0.001$). Likewise, T_G/GFR with caval obstruction was 3.3 mg/ml ±0.9, without caval obstruction in the same dogs T_G/GFR was 1.1 mg/ml ±0.3 ($P < 0.001$).

Since glucose reabsorption in the dog varies so markedly with changes in sodium reabsorption, any effect of GFR on glucose reabsorption could be obscured if sodium reabsorption were inconstant. Accordingly, the relationship of T_G to GFR was plotted (Fig. 1) using only those points associated with a fractional sodium excretion of 1% or less. Using values associated with such a narrow range of sodium reabsorption should effectively remove changes in sodium reabsorption as a regulating variable of glucose reabsorption. Absolute sodium excretion was also extremely low during these

TABLE III

Summary of Glucose Reabsorption

Dog	Weight	GFR	F_G	T_G	T_G/GFR	C_{Na}/GFR × 100	$U_{Na}V$
	kg	*ml/min*	*mg/min*	*mg/min*	*mg/ml*	*%*	*μEq/min*
1	11.7	25.5	226	27	1.1	18.6	616
2	10.4	33.9	265	17	0.5	31.7	1452
3	9.0	29.6	241	21	0.7	19.5	783
4	7.7	33.9	326	8	0.2	30.5	1404
5	10.6	18.7	230	42	2.2	0.9	22
6	10.1	26.3	167	3	0.1	38.2	1426
7	13.4	23.9	78	24	1.0	35.1	1183
8	9.8	17.7	192	80	4.5	0.1	3
9	10.0	16.6	212	58	3.5	0.8	17
10	12.5	51.8	383	38	0.7	25.7	1930
11*a*	15.0	54.7	219	167	3.0	0.5	39
11*b*	—	65.7	158	75	1.1	34.9	3301
12*a*	13.6	38.3	170	89	2.3	1.0	52
12*b*	—	59.8	341	39	0.7	27.8	2297
13*a*	7.6	15.2	135	60	3.9	0.6	12
13*b*	—	20.0	151	24	1.2	25.2	696
14	9.5	38.9	180	56	1.4	18.2	1018
15	7.6	21.4	158	16	0.7	27.3	842
16*a*	9.3	45.9	230	135	2.9	0.9	57
16*b*	—	62.4	232	80	1.3	30.2	2899
17*a*	8.3	18.9	182	82	5.3	0.2	6
17*b*	—	40.4	182	54	1.3	23.7	1408
18	10.4	42.0	213	123	2.9	0.7	40
19	10.1	53.1	288	165	3.1	0.7	47
20	7.4	26.7	171	81	3.0	0.3	12
21*a*	9.0	39.7	299	122	3.1	0.5	27
21*b*	—	24.7	244	25	1.1	19.1	640
22*a*	7.5	17.8	149	52	2.9	0.1	3
22*b*	—	29.1	174	37	1.3	13.2	532
23*a*	10.4	53.3	326	139	2.6	0.2	15
23*b*	—	36.7	439	63	1.7	14.5	676
24*a*	8.7	28.5	162	118	4.2	0.2	8
24*b*	—	34.7	264	21	0.6	33.8	1607
25*a*	9.9	30.9	202	83	2.7	0.1	5
25*b*	—	37.8	238	32	0.8	14.7	774
26	15.2	56.3	981	37	0.7	26.6	2175

periods; when fractional sodium excretion was in the range of 0.1 to 1%, absolute sodium excretion was in the range of 2–59 mEq/min. As is apparent from the Figure, glucose reabsorption under the circumstances just stipulated (plotted with ×'s), varies linearly with GFR. The regression line for these values is $Y = 7.07 + 2.66\ X$, $r = 0.93$ confirming the high degree of linearity. For purposes of comparison, values associated with ($[C_{Na}/GFR] \times 100 > 10\%$) are plotted using closed circles. These data points represent a much more heterogenous group ($[C_{Na}/GFR] \times 100$ 10–40%) and should not be as tightly grouped as those points associated with a less than 1% variation in fractional sodium excretion. Despite this, it is obvious that at any level of GFR, T_G is significantly higher in the group with higher sodium reabsorption. All points plotted on this graph are associated with a filtered load of glucose greater than one and a half times the rate of glucose reabsorption.

Fig. 2 demonstrates that this relationship of GFR to T_G holds true for an individual dog as well as from animal to animal. Of the 16 dogs studied with caval obstruction, 5 had unstable glomerular filtration rates. As the GFR fell in each dog there was a corresponding fall in glucose reabsorption even though filtered glucose did not fall and in some cases rose owing to an increase in glucose administration.

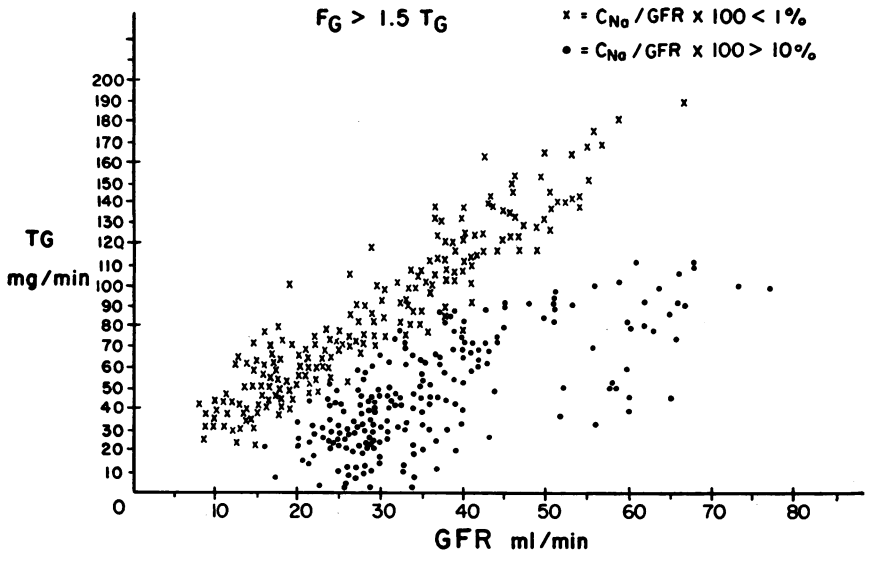

FIGURE 1 Glucose reabsorption (T_G) plotted against glomerular filtration rate (GFR). The X's are associated with fractional sodium excretion rates of less than 1%. The closed circles are associated with fractional sodium excretion rates of greater than 10%. All the data points are associated with a filtered load of glucose (F_G) greater than one and a half times the rate of glucose reabsorption.

To further define the relationship of glucose reabsorption to sodium reabsorption T_G/GFR was plotted against fractional sodium excretion (Fig. 3.) Again, all the values used were associated with filtered loads of glucose at least one and a half times the reabsorptive rate of glucose. This plot clearly demonstrates an inverse relationship between T_G/GFR and fractional sodium excretion.

DISCUSSION

This study demonstrates that glucose reabsorption in the dog is highly responsive to changes in both glomerular filtration rate and sodium reabsorption. Since no previous study has examined both these variables simultaneously, it is easy to understand why the effect of glomerular filtration rate on glucose reabsorption in the dog has not been previously recognized.

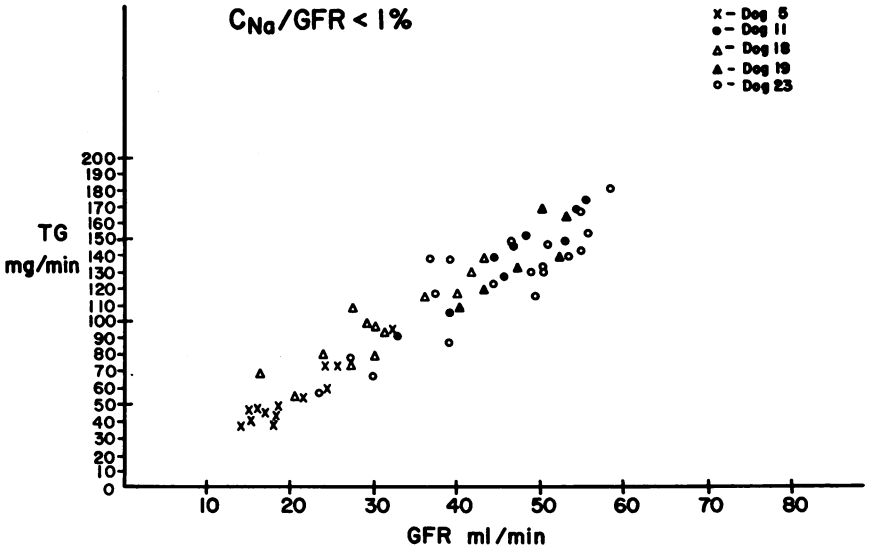

FIGURE 2 Glucose reabsorption is plotted against glomerular filtration rate using data from five dogs with decreasing glomerular filtration rate. Fractional sodium excretion was less than 1%. Filtered glucose was greater than one and a half times reabsorbed glucose.

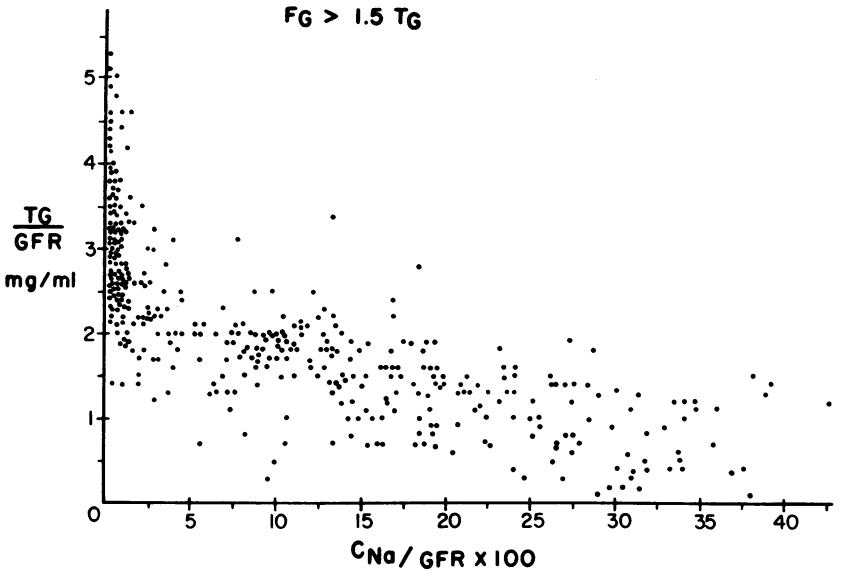

FIGURE 3 Glucose reabsorption expressed as milligrams per milliliter GFR is plotted against fractional sodium excretion.

Techniques used to depress glomerular filtration rate, such as controlled hemorrhage, can also be expected to stimulate proximal tubular sodium reabsorption. Thus, a stimulus for depressed glucose reabsorption would be counterbalanced by a stimulus for increased glucose reabsorption. When Thompson, Barrett, and Pitts (13) measured glucose reabsorption under such circumstances, no effect of reducing glomerular filtration rate on glucose reabsorption was noted until the filtration rate fell more than 50%. Obviously, T_G/GFR rose when glomerular filtration rate declined from 100 to 50%. From the data presented in our study, this should be associated with an increase in fractional sodium reabsorption. This assumption cannot be verified, however, since Thompson, Barrett, and Pitts did not measure sodium reabsorption in their study.

Shannon, Farber, and Troast (2) did not notice any effect on glucose reabsorption of changes in glomerular filtration rate. Again, sodium reabsorption was uncontrolled and the changes in filtration rate were of lesser magnitude than those produced by Thompson, Barrett, and Pitts (13). Our study demonstrates that when fractional sodium reabsorption is controlled over a narrow range, glomerular tubular balance for glucose exists and that this balance is disrupted when fractional sodium reabsorption changes.

Shannon and Fisher (1) showed a remarkably constant and reproducible Tm for glucose. The glomerular filtration rates of their dogs were extremely stable, no data concerning sodium reabsorption was presented, but if it were also constant, one would expect glucose reabsorption to be constant. Our data are in agreement with more recent studies (10, 11) of glucose reabsorption in the rat which have shown that glucose reabsorption varies with changes in glomerular filtration rate and sodium reabsorption. By plotting T_G/GFR against fractional sodium excretion we have fully defined the relationship of glucose reabsorption to sodium reabsorption. This relationship is very similar to that between bicarbonate reabsorption and fractional sodium excretion previously reported from this laboratory (4).

Since glucose reabsorption is limited to the proximal tubule, one would expect glucose reabsorption to be suppressed, in common with that of sodium, only when proximal tubular sodium reabsorption is suppressed. As sodium excretion increases owing to inhibition of sodium reabsorption in more distal parts of the nephron, one would expect little effect on glucose reabsorption. Examination of Fig. 3 demonstrates this phenomenon nicely. The major suppressive effect of increasing fractional sodium excretion on glucose reabsorption per unit GFR is noted from 0 to 5%. The major effect of volume expansion in inhibiting proximal sodium reabsorption is probably felt over this range of fractional sodium excretion. From 5 to 40%, fractional sodium excretion, glucose reabsorption falls, but at a much lesser rate.

When comparing glucose reabsorption with that of sodium, fractional sodium excretion is a much more meaningful index than is absolute sodium excretion. The former measures the efficiency of tubular sodium reabsorption, while the latter is influenced by the filtra-

tion rate as well as the efficiency of tubular reabsorption.

The mechanism by which sodium and glucose reabsorption are linked was not examined in this study. Robson, Srivastava, and Bricker (11) proposed that sodium and glucose might share a common transport system. An alternative hypothesis is that an increase in proximal tubular sodium reabsorption results in an increase in proximal tubular transit time, thus allowing proximal tubular urine containing glucose to remain in contact with the membrane (that of the proximal tubule) capable of reabsorbing glucose for a longer period of time, in turn resulting in increased glucose reabsorption assuming GFR to be constant. When there is a decrease in proximal tubular sodium reabsorption, the transit time falls, tubular urine is in contact with the glucose reabsorbing membrane for a shorter period of time, and glucose reabsorption decreases again assuming a constant GFR. This hypothesis also requires that glucose reabsorption does not exhibit saturation kinetics. A third possibility is that glucose passively diffuses through intercellular pores from lumen to blood. This passive diffusion is presumed secondary to the concentration gradient induced by sodium reabsorption. Further studies are necessary to determine which, if any, of these hypotheses is correct as well as to define the mechanism responsible for glomerular tubular balance for glucose.

Finally, it is obvious that the classical conception of tubular maxima must be reexamined. No substance that undergoes filtration and reabsorption can be considered without taking into account what is happening to the kidney as a whole. Reabsorption in the renal tubule is the result of not only the intrinsic capacity of the tubular membrane to transport the substance in question but is also the result of a number of modifying events the most potent of which is the rate of sodium reabsorption.

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