The Influence of Saline Loading on Renal Glucose Reabsorption in the Rat

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ABSTRACT Glucose titration studies were performed in normal rats under control conditions and during expansion of the extracellular fluid volume. In association with expansion, the maximal rate of glucose transport ($Tm_{glucose}$) *decreased* while glomerular filtration rate (GFR) typically increased; thus there was a consistent increase in the $GFR/Tm_{glucose}$ ratio. In previous studies, marked reduction of the nephron population was associated with an alteration in the kinetics of glucose transport and $GFR/Tm_{glucose}$ ratios were observed to increase. In both volume-expanded rats and in animals and human beings with uremia, the splay in the titration curve is increased. Finally in both volume-expanded animals and uremic animals fractional reabsorption of sodium is depressed. One interpretation of the present data is that the natriuretic "third factor" may influence a key rate-limiting step in glucose transport; and it is possible that this step is shared by or coupled to a rate-limiting step in sodium transport.

INTRODUCTION

The normal pattern of renal glucose excretion is altered markedly in patients with far advanced renal disease (1). The change is characterized by the excretion of appreciable quantities of glucose into the urine at blood sugar levels below those required to saturate the tubular reabsorptive capacity for glucose. This same change can be reproduced in animals by experimentally reducing the nephron population; its occurrence is independent of underlying renal disease since it is seen whether or not pathologic abnormalities are present in the remaining renal parenchyma (2). The mechanisms underlying the altered pattern of glucose excretion are not known; since the phenomenon occurs in uremic animals in which the residual nephrons are free of anatomic abnormalities and because the changes tend to be most marked in both man and animals with the greatest reduction in glomerular filtration rate (GFR), the possibility exists that adaptive changes in nephron function may induce modifications in glucose reabsorption. In this event, the alterations could have a kinetic explanation rather than one based either on a transport defect or on increased heterogeneity of the surviving nephrons.

One of the most pronounced changes in nephron function which occurs in chronic progressive renal disease is a decrease in fractional sodium reabsorption with an increase in sodium excretion rate per nephron. This natriuretic response in uremia has the same characteristics as the sodium diuresis observed in normal animals subjected to saline loading; it is not dependent upon an increase in GFR, nor does it require a decrease in mineralocorticoid activity. The natriuretic "third factor" which is thought to be primarily responsible for the natriuresis during saline loading has thus been invoked in explanation of the increased fractional excretion of sodium seen in uremia (3).

Since there is a considerable body of evidence that suggests some form of coupling between sodium transport and glucose transport in several different systems including the kidney (4–10), it is conceivable that the same factor that modifies

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proximal tubular reabsorption of sodium in uremia might initiate the changes in proximal tubular reabsorption of glucose. It so, saline loading in normal animals should alter the kinetics of glucose transport. This thesis has been examined experimentally in the present studies.

METHODS

Experiments were performed on normal unanesthetized female Sprague-Dawley rats of the Holtzman strain weighing between 240 and 280 g. Light ether anesthesia was maintained during the preparatory procedures. A 25 gauge needle attached to polyethylene tubing was secured in a tail vein for infusion of solutions. A PE 10 polyethylene catheter was inserted into one femoral artery to permit frequent sampling of arterial blood during the experiments. A PE 90 catheter was passed into the urinary bladder through the urethra and sutured in place. The anesthesia then was discontinued and the rat was placed in a bivalved plastic cylinder which contained a central hole through which the bladder catheter projected. The hind limbs projected through two lateral holes and the legs were taped to a horizontal bar placed below and at right angles to the cylinder.

A priming dose of carboxyl-^{14}C inulin was administered through the tail vein catheter and the sustaining dose of ^{14}C inulin dissolved in 100 mM NaCl solution was infused at a rate of 50 μl/min with a Harvard constant speed infusion pump. Simultaneously, 5% glucose in water was administered by a second pump at a rate of 96 μl/min. Both solutions were delivered into individual polyethylene tubes which joined the tail vein catheter at a Y-connection. A period of at least 1 hr was allowed for the animals to recover completely from the anesthetic. Thereafter one of two protocols was employed.

Control experiments. Both the glucose and saline infusions were continued at the same rate for an additional 60 min. Thereafter, urine collections were initiated and from 14 to 20 clearance periods were obtained, each of 20 min duration. The NaCl-inulin solution was delivered at a rate of 50 μl/min throughout the experiment. However, after two clearance periods were completed, the concentration of glucose in the second infusate was increased progressively in a stepwise fashion from the initial 5% to a value (usually 30%) sufficient to maintain a concentration of glucose in the urine of 2 g/100 ml (measured with glucose oxidase paper). Four to five clearance periods were obtained with this degree of glucosuria. Blood sugar values generally reached values of over 500 mg/100 ml with this regimen.

Volume expansion experiments. Extracellular fluid (ECF) was expanded before beginning the first clearance period according to the following schedule. A solution containing Na, 150 mEq/liter; K, 4 mEq/liter; Cl. 129 mEq/liter; and bicarbonate, 25 mEq/liter was infused at 190 μl/min for 20 min, 380 μl/min for 20 min, and 760 μl/min for 20 min. After this 60-min period of expansion, the rate of infusion was reduced to 380 μl/min and maintained at this level through the duration of the experiment. When the final delivery rate had been in effect for 20 min clearance periods were commenced. During the expansion periods and the first two clearance periods 5% glucose in water was infused at a rate of 63 μl/min. Subsequently, we increased the concentration of glucose progressively in the manner described for the control studies; in order to achieve comparable plasma glucose concentrations, we had to usually increase the concentration of infused glucose to 50%. 15–20-urine collection periods, each of 15 min duration, were obtained in most experiments. The glucose and saline solutions mixed before entering the animal and the final concentration of sodium in the infusate after the expansion was completed was 130 mEq/liter. The calculated rates of delivery of sodium and water were 57.8 μEq/min and 440 μl/min, respectively.

The glucose titration curves were constructed in the manner described by Smith et al. (11). The filtered load of glucose was plotted on the ordinate against glucose reabsorption ($T_{glucose}$) on the abscissa. Both terms were factored by the maximal rate of glucose transport ($Tm_{glucose}$) when comparison between animals was undertaken. Tm was calculated by averaging all values for $T_{glucose}$ after glucose reabsorption became relatively stable. In most experiments this involved averaging values for at least the final four to five clearance periods. The splay in the individual titration curves was calculated by accurately cutting the area of graph paper between the theoretical line of no splay and the observed titration curve and weighing the paper on an analytical balance. The mean "smoothed" titration curves for control studies and studies in saline loaded animals were calculated according to the method described by Smith (11). Additional details of the methods and procedures employed in this laboratory have been described in a previous paper (2).

When possible, both control and volume expansion experiments were performed on the same animals. An interval of 2 wk was allowed between studies and the order of the experimental sequence was randomized.

RESULTS

A total of 29 studies was completed on 16 rats. Several additional animals did not tolerate the high infusion rates required by the volume expansion protocol; in these animals, urine flow and sodium excretion increased initially but then fell and progressive positive sodium and water balance ensued. When this occurred, the experiment was terminated and data were not collected. In two rats, only control studies were performed and in four only volume expansion experiments were completed. All six of these animals died before we could perform a second study. We subjected the remaining 10 rats to both control and expansion studies and performed, in two of these animals,

studies during volume expansion on two or more occasions.

Detailed results are presented in Table I for the control and volume expansion studies on a representative animal. In the control experiment GFR averaged 2.73 ml/min. Plasma glucose concentrations increased progressively from approximately 200 mg/100 ml to a final value of over 500 mg/100 ml. Values for $T_{glucose}$ tended to stabilize over a blood sugar level of 350 mg/100 ml and the average glucose reabsorption rate for the last five clearance periods was 10.33 mg/min. This value represents the Tm.

During expansion of ECF volume the pattern was altered markedly. The average value for the GFR was 3.23 ml/min, an increase from the control study of 18.3%. Blood sugar concentrations increased in approximately the same progression as in the control studies, but the filtered load of glucose at any given plasma glucose concentration was greater due to the increase in GFR. Nevertheless, glucose reabsorption did not reach the same level as in the control study. Thus during the final six clearance periods, $T_{glucose}$ ranged from 7.77 to 8.31 mg/min and the value for $Tm_{glucose}$ was 8.08 mg/min. $Tm_{glucose}$, therefore, was *decreased* by 22% at the same time that GFR was *increased* by 18%. In the control experiment, the $GFR/Tm_{glucose}$ ratio was 0.26; in the volume expansion experiment the value was 0.40.

The transformation in the glucose titration curve produced by volume expansion is depicted in Fig.

TABLE I

Glucose Titration Experiments in a Representative Rat Studied under Control and Volume Expansion Conditions

Period No.	GFR	Plasma glucose	FL glucose	Glucose excretion	$T_{glucose}$	$\frac{FL}{Tm_g}$	$\frac{T_g}{Tm_g}$
	ml/min	*mg/100 ml*	*mg/min*	*mg/min*	*mg/min*		
1	2.69	210	5.65	0	5.65	0.55	0.55
2	2.75	206	5.67	0	5.67	0.55	0.55
3	2.64	223	5.89	0	5.89	0.57	0.57
4	2.68	226	6.06	0	6.06	0.59	0.59
5	2.73	264	7.21	0	7.21	0.70	0.70
6	2.89	299	8.64	0.08	8.56	0.84	0.83
7	2.74	331	9.07	0.0	9.07	0.88	0.88
8	2.86	365	10.44	0.53	9.91*	1.01	0.96
9	2.80	389	10.89	0.31	10.58*	1.05	1.02
10	2.68	498	13.35	2.05	11.30*	1.29	1.09
11	2.67	578	15.43	4.89	10.54*	1.49	1.02
12	2.68	585	15.68	6.38	9.30*	1.52	0.90
Mean	2.73			*$Tm_{glucose}$	10.33		
Volume expansion experiment							
1	3.27	150	4.91	0	4.91	0.61	0.61
2	3.39	179	6.07	0.02	6.05	0.75	0.75
3	3.11	196	6.10	0.01	6.09	0.75	0.75
4	3.00	188	5.64	0.04	5.60	0.70	0.69
5	3.24	234	7.58	0.18	7.40	0.94	0.92
6	3.18	246	7.82	0.81	7.01	0.97	0.87
7	3.29	284	9.34	1.57	7.77*	1.16	0.96
8	3.29	297	9.77	1.61	8.16*	1.21	1.01
9	3.36	300	10.08	1.84	8.24*	1.25	1.02
10	3.20	338	10.82	2.95	7.87*	1.34	0.97
11	3.26	403	13.14	4.83	8.31*	1.63	1.03
12	3.20	452	14.46	6.35	8.11*	1.79	1.00
Mean	3.23			*$Tm_{glucose}$	8.08		

GFR, glomerular filtration rate = inulin-^{14}C clearance; FL, filtered load glucose = GFR × plasma glucose concentration; Tg, glucose reabsorption; Tm_g and $Tm_{glucose}$, maximal rate of glucose transport.

* Denotes the values used to compute Tm.

1, in which the titration curve for the control and volume expansion experiments from a representative rat are compared. During the control experiment, approximately 1% of the filtered sodium was excreted before the advent of overt glycosuria. During the volume expansion study, 12.5% of the filtered sodium was excreted. As the filtered load of glucose was increased $T_{glucose}$ was *lower* during expansion. The maximum rate of glucose transport was markedly depressed during volume expansion with a $Tm_{glucose}$ value of 9.6 mg/min compared with a value of 11.4 mg/min in the control experiment, yet GFR was 22% higher in the volume expansion experiment. In consequence of these divergent changes in GFR and $Tm_{glucose}$, the GFR/Tm_g ratios averaged 0.26 in the control study and 0.37 in the expansion study. One other finding is implicit in Fig. 1. At any given filtered load, glycosuria was greater during volume expansion than in the control study; this difference became more marked at higher filtered loads.

A summary of all experiments performed on the 10 animals which were successfully studied during both control and volume expansion experiments is presented in Table II. GFR averaged 2.49 ml/min during control and 2.85 ml/min during expansion, it increased in eight animals but decreased in two. In both of the latter, sodium excretion rates remained brisk throughout the study and progressive positive sodium balance did not occur. Despite a mean increase in GFR for the group of 17.9%, Tm_g decreased from an average value of 9.68 mg/min during the control studies to 8.26 mg/min during volume expansion. The values for Tm_g were lower in 9 of 10 animals. In the 10th animal (No. 5, Table II) Tm_g was greater in absolute terms during expansion of ECF volume than during the control experiment, but the percentage increment in Tm was only 69% while GFR was increased by over 100%.[1] In the two animals in which GFR was lower during volume expansion (Nos. 9 and 10, Table II), Tm_g was decreased proportionately more. Thus in all animals the ratios for GFR/Tm_g were substantially higher during volume expansion. The mean value for the ratios during the control studies was 0.26; the mean value during

[1] The volume expansion study was performed first in this animal. Between studies a thigh abscess developed at the site of the first arterial catheterization. The clinical status in the second (control) study was poor and fractional excretion of sodium was low (0.2%) suggesting that the animal had a decreased GFR per nephron.

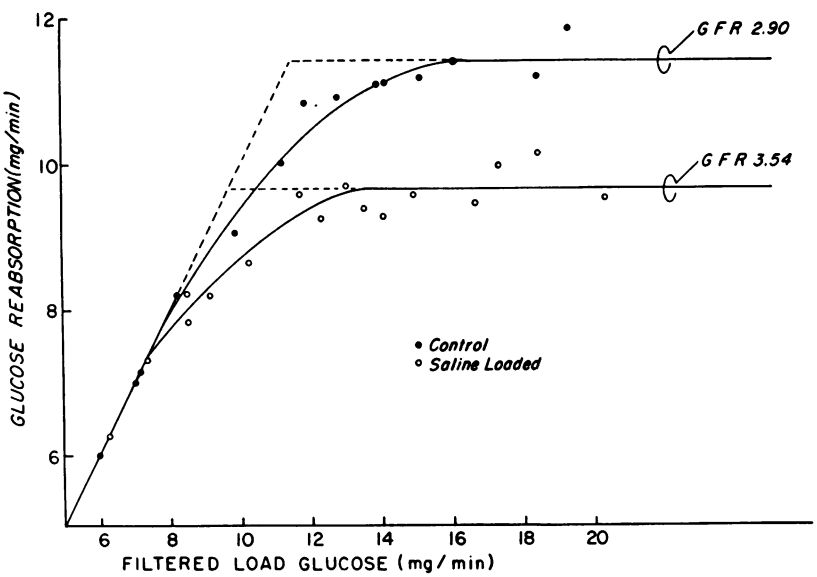

FIGURE 1 Glucose titration curves from one rat when studied under control conditions and after extracellular volume expansion. Fractional sodium excretion in the control experiment averaged 1.1% and during volume expansion the comparable value was 12.5%. The values for glucose are in absolute terms and are not factored by Tm.

TABLE II

Determinations of GFR, $Tm_{glucose}$, GFR/Tm_g Ratios, and Fractional Sodium Excretion in Rats Studied under Control Conditions and during Volume Expansion

Rat. No.	Glomerular filtration rate			$Tm_{glucose}$			GFR/Tm_g ratio		Maximum $\frac{FL}{Tm_g}$ values		Fractional Na excretion	
	Control	Volume expansion	Change	Control	Volume expansion	Change	Control	Volume expansion	Control	Volume expansion	Control	Volume expansion
	ml/min	*ml/min*	%	*mg/min*	*mg/min*	%	*ml/mg*	*ml/mg*			%	%
1	3.07	3.48	+13.3	11.53	10.37	−10.1	0.27	0.34	1.51	1.47	1.4	11.4
2	2.72	3.07	+12.9	10.70	9.95	− 7.0	0.25	0.31	1.97	1.37	4.7	11.4
3	2.52	3.06	+21.4	9.87	8.39	−15.0	0.26	0.36	1.25	1.86	1.0	12.3
4	2.27	2.69	+18.5	9.01	8.00	−11.2	0.25	0.34	1.33	1.33	2.1	12.9
5	1.62	3.45	+113.0	6.90	11.67	+69.1	0.23	0.30	1.55	1.60	0.2	13.1
6	2.90	3.54	+22.1	11.35	9.60	−15.4	0.26	0.37	1.72	2.12	1.1	12.5
7	2.18	2.95	+35.3	9.30	8.18	−12.0	0.23	0.36	1.14	1.49	1.7	12.0
8	2.73	3.23	+18.3	10.33	8.08	−21.8	0.26	0.40	1.52	1.79	2.5	15.0
9	2.52	1.94	−23.0	8.46	5.39	−36.3	0.30	0.36	1.63	1.56	1.4	8.6
10	2.41	1.13	−53.1	9.33	2.92	−68.7	0.26	0.39	1.57	2.18	2.4	25.1
Mean values	2.49	2.85	+17.9	9.68	8.26	−12.8	0.26	0.35	1.52	1.68	1.9	13.4

Fractional sodium excretion = the percentage of filtered sodium excreted.

volume expansion was 0.35. In the two animals in which only control studies were performed GFR/Tm_g ratios were 0.29 and 0.28. In the four animals studied only during volume expansion GFR/Tm_g ratios ranged from 0.33 to 0.39 with a mean of 0.35.

In addition to the divergent changes in Tm_g and GFR evoked by volume expansion, an increase in splay in the glucose titration curve also was observed. In each of the animals in which titration curves were available in both control and expansion studies, the splay was greater during expansion. The mean value for the control studies was 15.2 splay U while that for the expansion studies was 45.6 U. The increment for the group ranged from 10 to 70 U and averaged 29.6. Mean "smoothed" titration curves for the composite data obtained under the two sets of experimental conditions are presented in Fig. 2. The splay in the curve representing the volume expansion experiments is clearly greater than the curve from the control studies.

Table II also includes values for fractional sodium excretion. During control studies, fractional sodium excretion averaged 1.9%. During volume expansion, the values in the same animals ranged from 8.6 to 25.1% with a mean of 13.4%.

DISCUSSION

The present studies on normal rats demonstrate a marked change in the kinetics of glucose transport induced by ECF volume expansion. This observa-

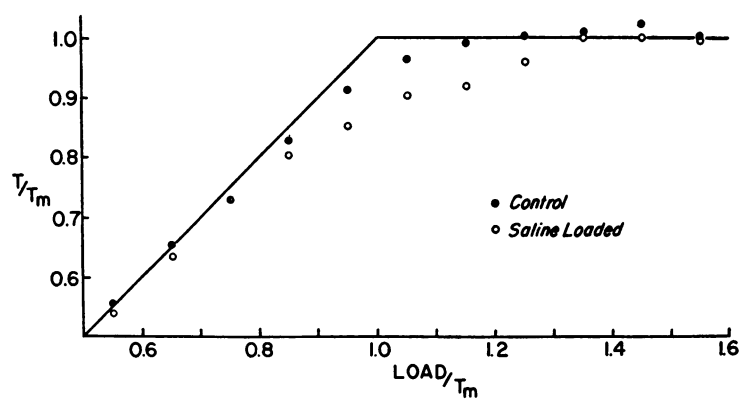

FIGURE 2 Mean glucose titration curves for the 10 animals studied under both experimental conditions. Values were calculated using the method of Smith (11). Load/Tm ratios above 1.6 are not shown in this plot, corresponding T/Tm values being close to 1.0.

tion is of intrinsic interest in terms of the biologic effects of volume expansion on proximal tubular function. It also may have some relevance to the changes in glucose reabsorption that occur in association with a marked reduction in the nephron population. Thus, the thesis proposed in the introduction, namely that the changes in glucose reabsorption in advanced renal disease might be initiated by the same factor(s) mediating the decrease in fractional sodium reabsorption receives some support from the present studies. The analogy between normal animals subjected to volume expansion and uremic animals is supported by several observations. (*a*) In both groups fractional sodium reabsorption is decreased. (*b*) The natriuretic "third factor" plays a major role in the change in fractional reabsorption during volume expansion (12) and the same factor has been invoked in the natriuresis per nephron in uremia (3). (*c*) In both groups, GFR (per nephron) typically increased. In uremic animals [2] as well as in saline loaded animals (13), GFR has been found to increase proportionately more in superficial cortical nephrons than in the whole kidney. (*d*) In both groups there is an increase in splay in the glucose titration curve. (*e*) In volume expanded animals $Tm_{glucose}$ decreases; in the animals subjected to nephron reduction $Tm_{glucose}$ increases, but to a degree proportionately less than the increase in GFR. Hence in both groups, GFR/$Tm_{glucose}$ ratios rise.

Glucose is actively transported by the proximal tubular epithelial cells. Presumably the transport is carrier mediated. The carrier may be assumed, therefore, to have a definable affinity for glucose, i.e. a K_m, and the reaction between carrier and glucose to have a maximum velocity. The decrease in $Tm_{glucose}$ in association with saline loading occurred under conditions wherein glucose concentrations were well in excess of those required to saturate the tubular transport capacity. $Tm_{glucose}$, therefore, should reflect the integrated activity of all of the potentially rate-limiting steps in transport, and the observed maximum rate of reabsorption should be determined by at least one of these rate-limiting steps; the latter could be at the site of entry of glucose into the epithelial cell, the carrier-glucose complex, or at an energy-producing step coupled to glucose transport. Therefore, some consequence of volume expansion, independent of GFR, may have affected a key rate-limiting step in the transport process. If the decrease in maximum velocity of glucose transport reflects alterations of an enzymatic step, it is conceivable that a natriuretic "hormone" (12) may have acted as a noncompetitive inhibitor. Because transport of glucose completely across tubular epithelial cells is not strictly analogous to a simple enzymic reaction, or even to a simple transport process (such as potassium entry into a red cell), classic Michaelis-Menton analyses cannot be applied with confidence; thus K_m measurements cannot be determined satisfactorily with glucose titration data.[3] Accordingly the suggestion of noncompetitive inhibition, which would require no change in K_m with a decrease in V_{max} cannot be examined more rigorously.

Other explanations for the change in glucose transport during volume expansion must also be entertained. Intrarenal alterations of blood flow and a preferential increase in GFR per nephron in the cortical nephrons could lead to an increase in nephron heterogeneity and thus to an increase in splay in the titration curve. However, on a priori grounds, hyperfiltration in the predominant population of nephrons should not decrease $Tm_{glucose}$; thus, in theory an increase in GFR per nephron at high plasma glucose levels should produce either no change in the rate of glucose reabsorption or if there is glomerulo-tubular balance for glucose, glucose reabsorption should increase. Hence an additional mechanism would still have to be invoked. A change in renal interstitial fluid volume in relation to tubular volume might influence glucose transport in the same manner that has been suggested in the case of sodium (15).[4] Still another possibility is that a decrease in fractional

[2] Lubowitz, H., M. L. Purkerson, and N. S. Bricker. Unpublished observations.

[3] Burgen (14) has discussed the application of Michaelis-Menton equations to standard glucose titration data and the reader is referred to his paper for his evidence suggesting that the K_m for a carrier-substrate complex must be extremely low.

[4] Smith (11) observed a decrease in $Tm_{glucose}$ in two normal subjects after saline loading. He suggested that this might relate to an increase in renal interstitial fluid and an increase in intrarenal pressure with reduction or cessation of filtration in some nephrons and compensatory hyperfiltration in others.

water reabsorption in the proximal tubule led to a decrease in tubular fluid concentration of glucose. This seems unlikely, however, for when the filtered load of glucose is about two times the $Tm_{glucose}$, as it was in several of the present animals, the concentration of glucose in the tubular fluid probably does not decrease by more than 25 to 50% en route down the proximal tubule. Thus half of the glucose molecules are reabsorbed and under the conditions of these experiments (fractional sodium excretion averaged 13.4%) at least one out of four water molecules should be reabsorbed proximally. Finally an explanation based on increase in velocity of tubular flow also is unlikely for mannitol diuresis, with a comparable excretion of filtered salt and water, does not reproduce the effects of volume expansion.[5]

If there is a common step in the transport of glucose and sodium in the mammalian nephron and if a natriuretic hormone influences this step, then glucose transport might serve as a model for exploring some aspects of sodium reabsorption; glucose presents one major experimental advantage, it may be studied over a wide range of concentrations and its kinetics defined with some precision. In contrast to this, sodium concentrations can be varied only over a very limited range particularly in the upward direction.

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