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EFFECTS OF PREGNANCY ON GLUCOSE REABSORPTION BY THE PROXIMAL CONVOLUTED TUBULE IN THE RAT

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SUMMARY

1. Free-flow micropuncture techniques were used to investigate glucose, sodium and water reabsorption along the proximal convoluted tubule in 7–8 day pregnant rats undergoing saline or glucose infusion and in virgin controls.

2. Absolute proximal tubular reabsorption of glucose was greater in pregnant animals than virgins during both saline and glucose infusion; and fractional reabsorption of glucose was higher in pregnant than in virgin animals during glucose infusion.

3. During glucose loading, less glucose escaped reabsorption in the proximal tubule in pregnant than in virgin animals. It is concluded that the increased excretion of glucose observed in pregnant rats cannot be due to failure of proximal tubular mechanisms.

4. During saline infusion pregnant animals had a higher single nephron glomerular filtration rate (S.N.G.F.R.) when compared with virgin animals and a corresponding increase in reabsorption of sodium and water. The small increases in S.N.G.F.R. and sodium reabsorption in pregnant animals (compared with virgin animals) during glucose infusion were not statistically significant.

5. Fractional reabsorption of sodium (and water) along the proximal convoluted tubule was not significantly different in the four series. It is concluded that glomerulo-tubular balance operates during pregnancy.

INTRODUCTION

Pregnancy is associated with major changes in renal function. These have been documented best in humans (see Hytten & Leitch, 1971) but qualitatively similar changes have been described in rats with respect to alterations in glomerular filtration rate (G.F.R.) (Matthews & Taylor, 1959; Lindheimer & Katz, 1971; Atherton & Pirie, 1977; Bishop & Green, 1980), increased salt and water reabsorption (Lichton, 1963; Lichton & Hugh, 1968; Katz & Lindheimer, 1973; Atherton & Pirie, 1977; Bishop & Green, 1980) and increased amounts of glucose in the urine (Bishop & Green, 1980).

The increased urinary glucose loss in pregnant women has been ascribed to either

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an increased filtered load of glucose overloading the normal reabsorptive capacity of the proximal tubule (Christiansen, 1958) or to a decreased reabsorptive capacity of the proximal tubule (Welsh & Sims, 1960). Neither of these hypotheses has been tested by direct micropuncture analysis of proximal tubular function. Furthermore, Bishop & Green (1979*a*, *b*) have presented data to show that transport of glucose by segments of the nephron other than the proximal convoluted tubule may be changed during pregnancy.

The present study was designed to investigate directly reabsorption of glucose by the proximal tubule, under conditions of normal and elevated plasma glucose concentrations in virgin and pregnant rats. In addition the study also provided data on salt and water handling.

METHODS

Experiments were performed on female Sprague–Dawley rats all aged 12–13 weeks; sixteen were virgin animals and twenty-three in the 7–8 day of pregnancy (timed from the appearance of the cervical mucus plug on the floor of the cage). They were prepared for micropuncture as described previously (Bishop, Green & Thomas, 1978). Briefly, animals were anaesthetized by an I.P. injection of 120 mg . kg^{-1} body weight of Inactin (5-ethyl-5-(1′-methyl-propyl)2-thiobarbiturate) and placed on a thermostatically heated operating table set to maintain body temperature at 38 °C. Catheters were inserted into the left jugular vein for infusion of fluids and into the right carotid artery to record systemic blood pressure (using a Statham P 23 DC transducer and a Grass P7 polygraph). Tracheostomy ensured a clear airway. The left kidney was exposed through a flank incision and placed in a perspex holder to minimise movements of the kidney due to respiratory movement of the diaphragm. The left ureter was catheterized to ensure free flow of urine and care was taken that the blood supply to the kidney was not impeded.

Saline (150 m-mole . $l.^{-1}$) was administered I.V. as a priming dose of 1 ml. (containing [^{3}H]inulin, 20 μc . $ml.^{-1}$) to compensate for fluid losses during surgery and as a continuous sustaining infusion (200 μl . min^{-1} containing 5 μc . $ml.^{-1}$ [^{3}H]inulin). After 4 hr, the infusion was changed to 5% D-glucose (200 μl . min^{-1} containing 5 μc . $ml.^{-1}$ [^{3}H]inulin) for a further 3 hr. The first 90 min of saline infusion and 30 min of glucose infusion were allowed for equilibration (see Bishop & Green, 1980) and thereafter, micropuncture samples were collected from randomly selected proximal tubules as described previously (Bishop, Green & Thomas, 1979). One to three tubules were punctured during each infusion in each animal. Tubules were drawn for later identification. Blood samples (50 μl.) were collected from a tail vein, into heparinized haematocrit tubes every 30 min throughout the experiment and at its termination.

At the end of the experiment, the punctured tubules were re-identified and filled with Microfil (Canton Biomedical Products Inc., Boulder, Colorado, U.S.A.); the kidney was removed and stored overnight in deionized water at 4 °C. Next day, after partial digestion of the kidney in 10% sodium hydroxide, the casts of the tubules were dissected out, drawn and measured as previously described (Bishop *et al.* 1979).

Analyses

The volume of fluid collected from each puncture site was measured in a calibrated constant bore capillary of approximately 0·3 mm internal diameter. Aliquots of tubular fluid and plasma were taken for [^{3}H]inulin analysis in a liquid scintillation counter with P.C.S. (Radiochemical Centre, Amersham), diluted 1 : 1 with A.R. toluene, as a scintillant. Plasma and tubular fluid concentrations of sodium were measured on a Helium Flow Photometer (Aminco Inc., Silver Springs, Maryland, U.S.A.) and glucose was measured using an enzymatic technique (Bishop *et al.* 1978) reading the fluorescent emission on a fluoromicrophotometer (Aminco Inc., Silver Springs, Maryland, U.S.A.).

Calculations

Single nephron glomerular filtration rate, S.N.G.F.R = $V\,(TF_{in}/P_{in})$.

Nephron filtered load = S.N.G.F.R. . P_A.

Reabsorptive flux of water = $V((TF_{in}/P_{in})-1)$.

Reabsorptive flux of solute = (S.N.G.F.R. . P_A) $- V\,.\,TF_A$).

Fractional excretion = $(TF_A/P_A)/(TF_{in}/P_{in})$.

Fractional reabsorption = 1 − fractional excretion.

Where V = volume of fluid collected in unit time; TF_{in}/P_{in} = ratio of inulin counts in tubular fluid and plasma; and P_A and TF_A = concentrations of A in plasma and tubular fluid respectively.

Results are presented as mean ± S.E. of mean and the significance of differences are calculated using Student's t test.

RESULTS

As in previous reports (Bishop & Green, 1980; Garland, Green & Moriarty, 1978), pregnant animals were significantly heavier than comparably aged virgins (240 ± 5 g pregnant, 170 ± 4 g virgin; $P < 0{\cdot}001$) but there was no significant difference in mean systemic blood pressure which in all cases was greater than 100 mmHg. Again as reported previously (Bishop & Green, 1980), during periods in which the punctures were performed there were no significant changes in plasma sodium and glucose concentrations and, therefore, detailed time courses are not presented; the mean value for each animal for each infusion was calculated from the three to four plasma samples obtained and the means and standard errors computed for each series (Table 1).

Single nephron filtration rates, S.N.G.F.R. (Table 1), were not significantly different when the values obtained during saline infusion were compared with those obtained during glucose infusion in either virgin or pregnant animals. There was a significantly higher S.N.G.F.R. in pregnant animals than in virgins during saline infusion ($P < 0{\cdot}001$); but during the glucose infusion, the small increase in pregnant animals was not statistically significant.

Glucose

Plasma glucose concentration was not significantly different in virgins and pregnant animals during either the saline or the glucose infusion (Table 1). Glucose infusion, of course, significantly raised the plasma glucose concentration in both virgin and pregnant animals. Together with the changes in S.N.G.F.R. this means that during saline infusion, pregnant animals filtered more glucose per nephron than virgin controls, but during glucose infusion the amounts filtered by virgins and pregnant animals were not significantly different (Table 1).

As expected, in both virgins and pregnant animals during saline infusion, the concentration of glucose in collected proximal tubular fluid was low and there was no significant difference in the tubular fluid to plasma glucose concentration ratio (TF/P glucose; Table 2). During glucose infusion however, when plasma glucose was always in excess of 15 m-mole . $l.^{-1}$, TF/P glucose in virgins was not significantly different from 1; this would be expected from other workers' data (see Discussion). However, in pregnant animals with similar plasma glucose concentrations the TF/P glucose was significantly reduced to 0·68.

The reabsorptive fluxes of glucose plotted against the distance of the puncture site from the glomerulus are shown in Fig. 1. During saline infusion in both virgin (Fig.

1 *A*) and pregnant animals (Fig. 1 *B*) there was no correlation between length of tubule over which reabsorption occurred and glucose reabsorption; the horizontal line in Figs. 1 *A*, *B* represents the mean ± S.E. of mean of the amount of glucose reabsorbed. It is obvious that during saline infusion pregnant animals reabsorbed more glucose than virgin animals (Fig. 1, Table 2).

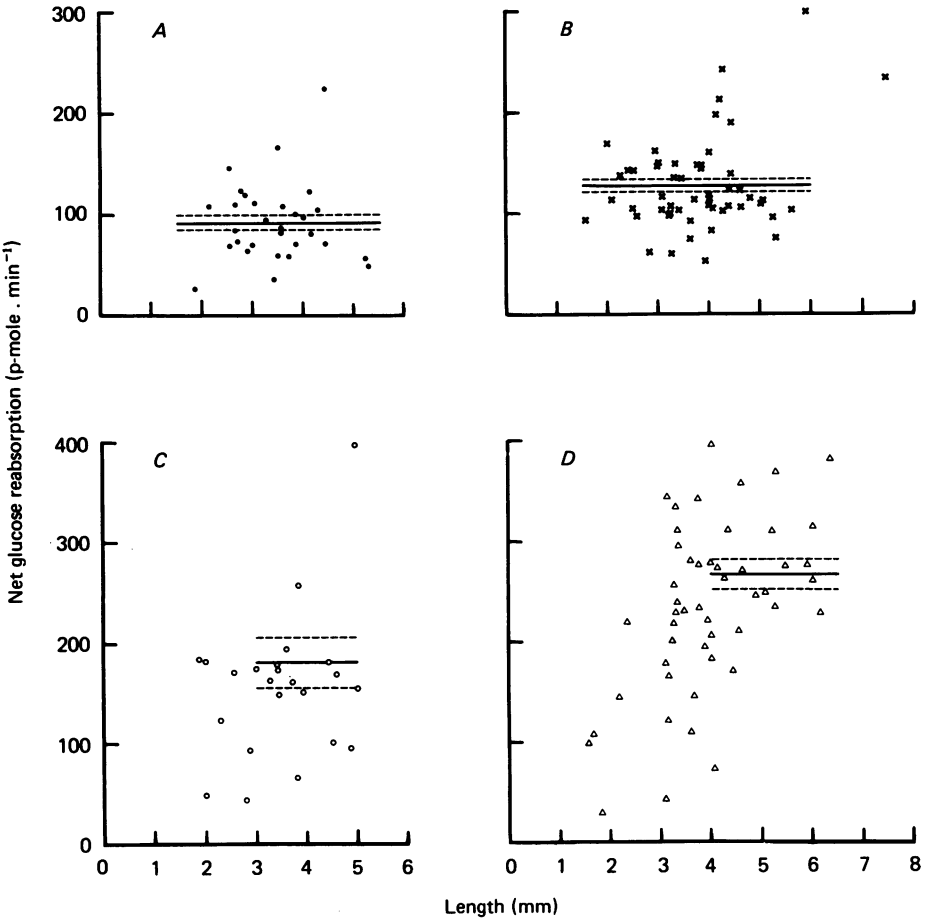

Fig. 1. Glucose reabsorption along the length of the proximal convoluted tubule in virgin animals during saline (*A*) and glucose infusion (*C*) and 7–8 day pregnant animals during saline (*B*) and glucose infusion (*D*). Horizontal lines represent mean ±1 S.E. of mean over the distance indicated.

The data in Fig. 1 *C*, *D* could be fitted by a linear regression equation calculated using the least squares method; for the virgin animals receiving glucose the net glucose reabsorptive flux = 32·6 length + 48·5 ($r = 0{\cdot}42$, $n = 23$, $P < 0{\cdot}05$) and for the pregnant animals receiving glucose net glucose reabsorptive flux = 43·5 length + 56·1 ($r = 0{\cdot}54$, $n = 50$, $P < 0{\cdot}001$). This would suggest that the reabsorption in pregnant animals was greater than in virgin animals. However because of the pattern of glucose

TABLE 1. Single nephron G.F.R., plasma concentrations and filtered loads of sodium and glucose in virgin and pregnant rats

	Virgin			Pregnant		
	Saline infusion	Glucose infusion	P_1	Saline infusion	Glucose infusion	P_2
n	31	25		54	50	
S.N.G.F.R. (nl. min^{-1})	$19{\cdot}3 \pm 1{\cdot}2$	$22{\cdot}5 \pm 1{\cdot}5$	n.s.	$27{\cdot}21 \pm 1{\cdot}13$***	$27{\cdot}5 \pm 1{\cdot}0$	n.s.
Plasma Na (m-mole . $l.^{-1}$)	$150{\cdot}5 \pm 1{\cdot}9$	$143{\cdot}2 \pm 1{\cdot}8$	$< 0{\cdot}01$	$149{\cdot}0 \pm 3{\cdot}0$	$138{\cdot}3 \pm 1{\cdot}8$	$< 0{\cdot}01$
Filtered load of sodium (p-mole . min^{-1})	2885 ± 172	3258 ± 243	n.s.	4044 ± 212***	3580 ± 165	n.s.
Plasma glucose (m-mole . $l.^{-1}$)	$5{\cdot}09 \pm 0{\cdot}30$	$21{\cdot}02 \pm 1{\cdot}22$	$< 0{\cdot}001$	$5{\cdot}01 \pm 0{\cdot}16$	$19{\cdot}40 \pm 0{\cdot}16$	$< 0{\cdot}001$
Filtered load of glucose (p-mole . min^{-1})	$98{\cdot}7 \pm 8{\cdot}7$	$490{\cdot}4 \pm 42{\cdot}7$	$< 0{\cdot}001$	$137{\cdot}9 \pm 6{\cdot}5$***	$486{\cdot}3 \pm 18{\cdot}5$	$< 0{\cdot}001$

P_1 is the probability that the differences between saline and glucose infusion in virgin animals arose by chance.

P_2 is the probability that the differences between saline and glucose infusion in pregnant animals arose by chance.

The probability of differences between virgin and pregnant animals arising by chance is shown by asterisks. *, $P < 0{\cdot}05$, **, $P < 0{\cdot}01$, ***, $P < 0{\cdot}001$.

n is the number of tubules punctured.

TABLE 2. Glucose reabsorption in virgin and pregnant rats

	Virgin			Pregnant		
	Saline infusion	Glucose infusion	P_1	Saline infusion	Glucose infusion	P_2
$TF/P_{glucose}$	0·120 ± 0·029 (31)	0·986 ± 0·036 (25)	< 0·001	0·95 ± 0·012 (54)	0·684 ± 0·029*** (50)	< 0·001
Glucose reabsorbed at 'equilibrium' (p-mole . min^{-1})	91·9 ± 7·7 (31)	180·1 ± 24·5 (16)	< 0·001	127·9 ± 6·3*** (54)	265·9 ± 15·1** (23)	< 0·001
% Glucose reabsorbed at 'equilibrium'	93·9 ± 0·99 (31)	38·3 ± 2·73 (16)	< 0·001	92·8 ± 1·03 (54)	58·5 ± 3·39*** (23)	< 0·001
Glucose not reabsorbed in tubules punctured > 4 mm from glomerulus. (p-mole . min^{-1})	8·1 ± 2·9 (8)	390·7 ± 66·9 (6)	< 0·001	7·9 ± 2·2 (25)	202·0 ± 25·0*** (23)	< 0·001

Numbers in parentheses are the numbers of tubules.

P_1 P_2 and * see Table 1.

N.b. 'Equilibrium' is defined as the state in later parts of the tubule where there is no significant correlation between the glucose reabsorbed and the distance of the puncture site from the glomerulus.

reabsorption in the proximal tubule this may not be the most appropriate analysis to perform (see Bishop *et al.* 1979). Accordingly we have taken later parts of the tubule and checked where there was *no* correlation of glucose flux with length and called this the 'equilibrium' value. In virgin animals perfused with glucose this was in punctures more than 3 mm from the glomerulus and in pregnant animals in punctures greater than 4 mm from the glomerulus. This stable or 'equilibrium' value was greater in pregnant than in virgin animals. Analysis of mean glucose reabsorption in successive

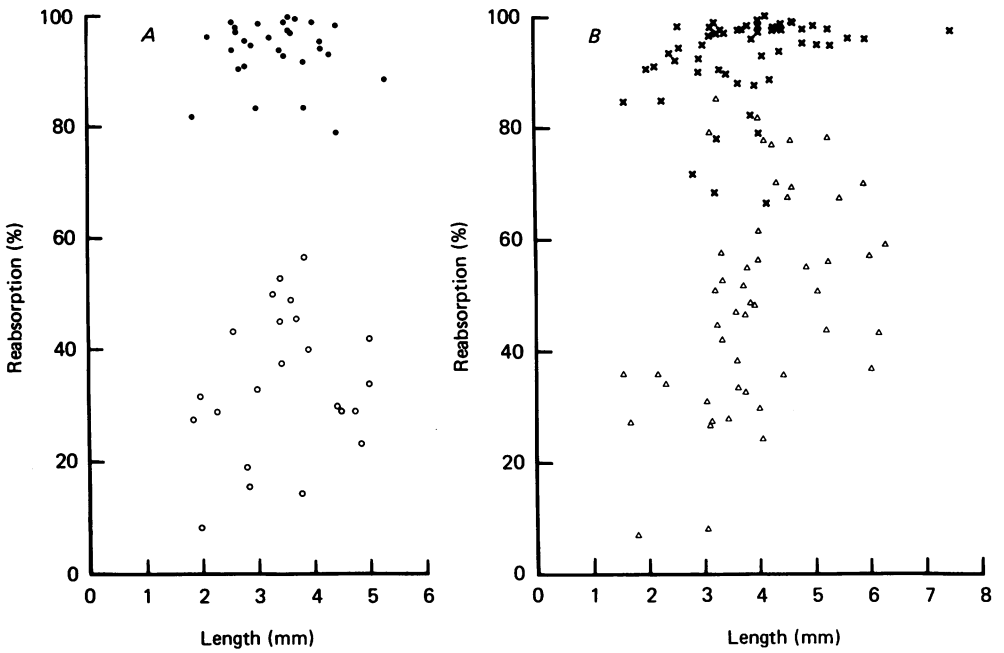

Fig. 2. Fractional reabsorption of glucose along the length of the proximal convoluted tubule in virgin animals (*A*) undergoing saline (●) or glucose (○) infusion, and pregnant animals (*B*) undergoing saline (×) or glucose (△) infusion.

millimetre segments of the proximal tubule confirmed this finding; e.g. while there was no significant difference in mean glucose reabsorption in punctures situated 3–4 and 4–5 mm from the glomerulus in virgin animals undergoing glucose infusion, mean glucose reabsorption between 2 and 3 mm was significantly less than either. The findings are reinforced when the percentage (or fractional) reabsorption of glucose is considered (Fig. 2). During saline infusion, more than 90% of the filtered glucose was reabsorbed by both virgin and pregnant animals (Table 2). During glucose infusion, percentage reabsorption was much less in both virgin and pregnant animals; but if longer segments of the tubule are considered (i.e. those where there is no further correlation of net glucose flux and length) pregnant animals reabsorb a much greater percentage (58·5%) than do virgins (38·3%; see Table 2).

Because distal segments of the nephron can also reabsorb glucose, the amount of glucose which escapes reabsorption in the proximal tubule, and is consequently

available for reabsorption by later segments, is also of interest. We have taken this as that glucose which has not been reabsorbed at puncture sites more than 4 mm from the glomerulus, since at this distance all series had reached an 'equilibrium' value.

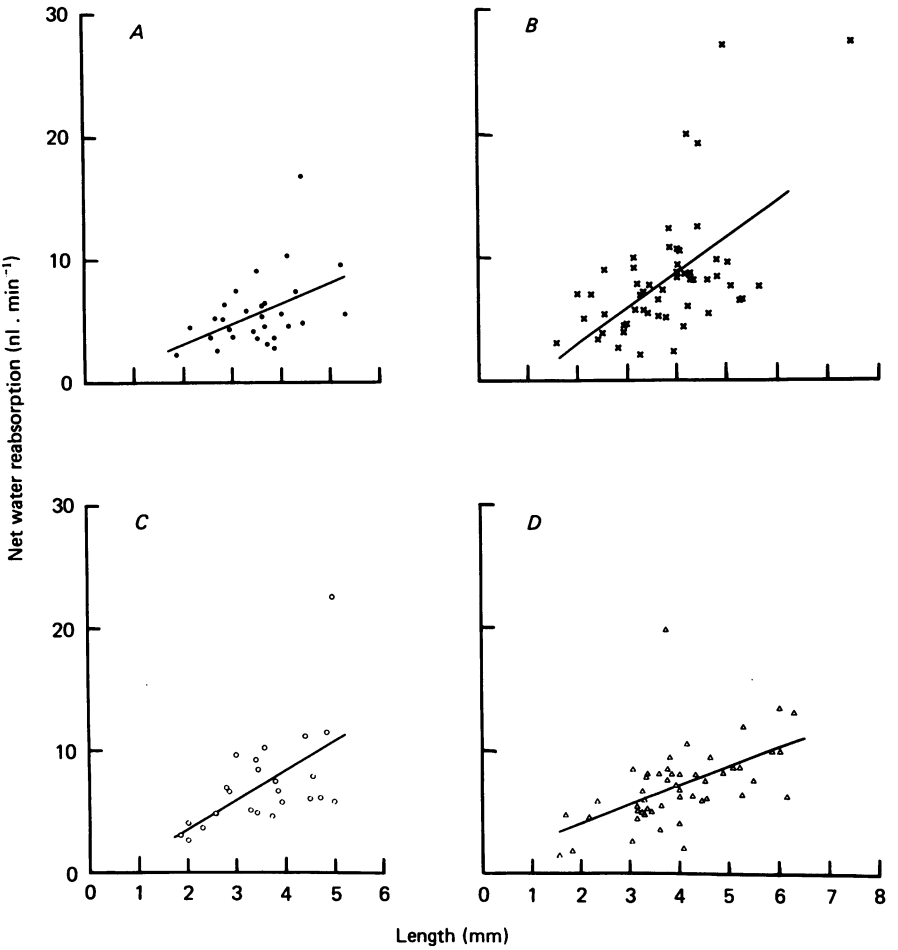

Fig. 3. Net water reabsorption along the length of the proximal convoluted tubule in virgin animals during saline (*A*) or glucose (*C*) infusion and pregnant animals during saline (*B*) or glucose (*D*) infusion. The lines are the calculated lines of best fit. The regression equations are (*A*) net water reabsorption = 1·65 length −0·17; $r = 0{\cdot}453$, $P < 0{\cdot}01$; (*B*) net water reabsorption = 2·89 length −2·73; $r = 0{\cdot}612$, $P < 0{\cdot}001$; (*C*) net water reabsorption = 2·38 length −1·13; $r = 0{\cdot}571$, $P < 0{\cdot}01$; (*D*) net water reabsorption = 1·55 length +1·05; $r = 0{\cdot}549$, $P < 0{\cdot}001$. Slopes of the regression lines in *A*, *C* and *D* are not significantly different. The slope of the line in *B* is significantly different from either *A* or *C* ($P < 0{\cdot}01$).

On this basis, there was no significant difference in the amount passed on to the pars recta of the proximal tubule in virgins and pregnant animals during saline infusion; whereas during glucose infusion, much less was passed on in pregnant animals than in virgins (Table 2). Since proximal tubules are longer in pregnant animals than

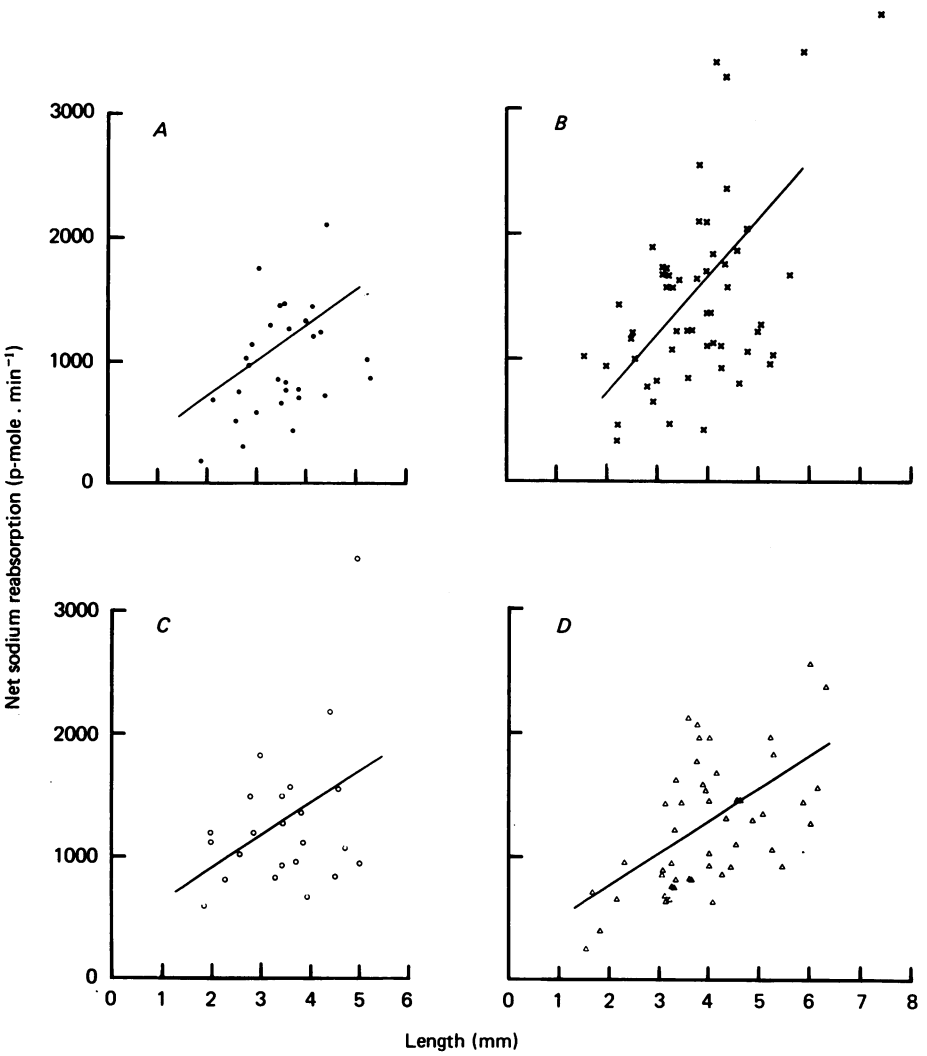

Fig. 4. Net sodium reabsorption along the length of the proximal convoluted tubule in virgin animals during saline (*A*) or glucose (*C*) infusions and pregnant animals during saline (*B*) or glucose (*D*) infusions. The lines are the calculated lines of best fit. The regression equations are (*A*) net sodium reabsorption = 228 length +148; $r = 0{\cdot}415$, $P < 0{\cdot}05$; (*B*) net sodium reabsorption = 481 length −319; $r = 0{\cdot}577$, $P < 0{\cdot}001$; (*C*) net sodium reabsorption = 258 length +388; $r = 0{\cdot}397$, $P < 0{\cdot}05$; (*D*) net sodium reabsorption = 260 length +260; $r = 0{\cdot}482$, $P < 0{\cdot}001$. Slopes of the regression lines in *A*, *C* and *D* are not significantly different. The slope of the line in *B* is significantly different from either *A* or *C* ($P < 0{\cdot}01$).

virgins (Garland *et al.* 1979), this way of expressing results will tend to minimize any real differences between virgins and pregnant animals. It thus seems certain that no more glucose escapes reabsorption in the proximal convoluted tubules in pregnant animals than in virgins, whether saline or glucose is being infused.

TABLE 3. Water and sodium reabsorption in virgin and pregnant rats

	Virgin			Pregnant		
	Saline infusion	Glucose infusion	P_1	Saline infusion	Glucose infusion	P_2
TF/P_{Na}	0·942±0·019	0·881±0·017	< 0·05	0·919±0·011	0·899±0·012	n.s.
Water reabsorbed in unit length. (nl . min^{-1}. mm^{-1})	1·642±0·124	2·030±0·155	n.s.	2·148±0·124**	1·827±0·0102	n.s.
Sodium reabsorbed in unit length. (p-mole . min^{-1}. mm^{-1})	312±31	365±30	n.s.	397±23*	329±20	< 0·05

Water and sodium reabsorption were calculated by factoring net water (or sodium) reabsorption flux by the length of tubule over which reabsorption had occurred.

P_1, P_2 and * see legend to Table 1.

Water and sodium

Water reabsorption in tubules from both virgin and pregnant animals during saline and glucose infusion correlated significantly with the distance of the puncture site from the glomerulus (Fig. 3). Statistically, there was no significant difference between

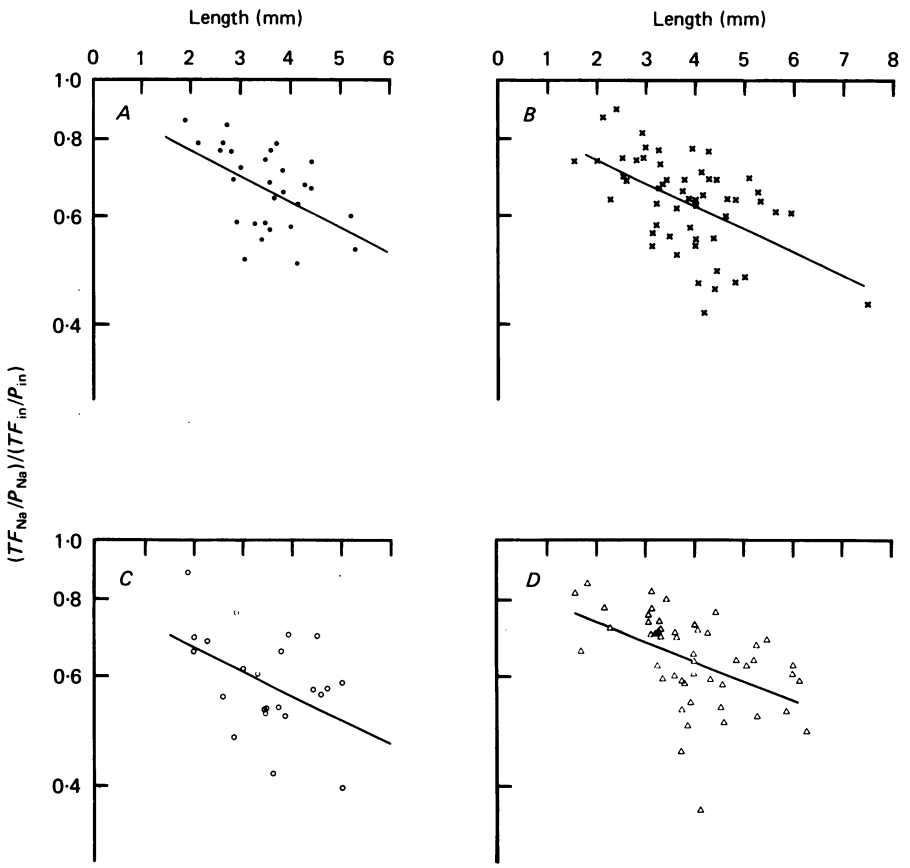

Fig. 5. Fractional excretion of sodium along the length of the proximal convoluted tubule in virgin rats during saline (*A*) and glucose (*C*) infusions and in pregnant rats during saline (*B*) and glucose (*D*) infusions. The lines are the calculated lines of best fit. The regression equations are (*A*) log fractional excretion of sodium = −0·042 length −0·033; $r = -0{\cdot}505$, $P < 0{\cdot}005$; (*B*) log fractional excretion of sodium = −0·037 length −0·059; $r = -0{\cdot}529$, $P < 0{\cdot}001$; (*C*) log fractional excretion of sodium = −0·038 length −0·097; $r = -0{\cdot}455$, $P < 0{\cdot}02$; (*D*) log fractional excretion of sodium = −0·032 length −0·070; $r = -0{\cdot}489$, $P < 0{\cdot}01$. The slopes of the regression lines were not significantly different from each other.

the slopes of the regression line for the virgin animals during saline and glucose infusion or the pregnant animals during glucose infusion; however, the slope of the regression line for pregnant animals during saline infusion was significantly different than that for virgin animals during saline infusion ($P < 0{\cdot}01$). In no series was there evidence of an equilibrium value for sodium reabsorption as described for glucose

reabsorption. Another way of calculating the reabsorptive flux is to take the net flux and divide it by the length of tubule which is reabsorbing the water. This makes the assumption that fluid reabsorption in the first part of the nephron, which is not accessible to conventional micropuncture, is similar to that in the remainder of the nephron; this assumption is not inherent in the use of the regression line and is the reason why there are differences in absolute values in the rate of reabsorption calculated by the two methods (compare slope of lines in Fig. 3 with values in Table 3). Even allowing for this difference between the two methods of expressing water reabsorption per unit length, exactly the same pattern of results was found (Table 3): i.e. the reabsorptive rate was only significantly different between virgin and pregnant animals during saline diuresis.

Sodium reabsorption (Fig. 4; Table 3) followed essentially the same pattern. There was a significant increase in sodium reabsorption in pregnant animals, when compared with virgins, during saline infusion (Fig. 4), and this was confirmed by the reabsorption rate for sodium (Table 3). When the *fraction* of filtered sodium remaining in the tubular lumen was plotted against length however (Fig. 5), there were no significant differences in slope of the lines, indicating that fractional excretion (and hence fractional reabsorption) was not significantly altered. The same was found for fractional water reabsorption (so the data are not presented).

In all series, the tubular fluid to plasma sodium concentration ratio, TF/P_{Na}, was significantly lower than 1 (Table 3) confirming earlier observations in male animals (see Table 2 in Bishop *et al.* 1979); but while TF/P sodium was significantly lower during glucose than during saline infusion in virgins, pregnancy caused no significant changes either during saline or glucose loading.

DISCUSSION

With respect to glucose handling, the main findings in the present study are: first, that proximal tubular glucose reabsorption is increased in pregnant animals when compared with virgins, during both saline and glucose infusion; secondly, that delivery of glucose to distal parts of the nephron is no higher in pregnant animals than in virgins; thirdly, that even at low glucose concentrations, less than 95% of the filtered glucose was reabsorbed by the end of the proximal tubule. Qualitatively the results obtained in virgin animals are similar to the results in males (Bishop *et al.* 1979) in spite of quantitative differences which could be attributed to the different protocol employed and the sex of the animal.

These experiments were not specifically designed to investigate changes in G.F.R. or redistribution of filtration between cortical and deep nephrons, so whole kidney G.F.R. was not measured. However, the changes in S.N.G.F.R. during saline infusion in pregnant animals are similar in pattern to the whole kidney G.F.R. changes previously reported (Bishop & Green, 1980). On this basis, there is no evidence for intrarenal redistribution of glomerular filtration; but a stricter analysis must depend on experiments where S.N.G.F.R. and whole kidney G.F.R. are measured at the same time.

Glucose

The conventional description of glucose handling by the mammalian kidney is of reabsorption in the early part of the proximal convoluted tubule up to a limiting maximum – the tubular maximum for glucose (T_{mG}). When plasma glucose levels are normal, then the reabsorptive capacity of the tubule is sufficient to ensure a glucose-free urine; but when a certain threshold level is exceeded, T_{mG} is correspondingly exceeded and glucose spills over into the urine. This conventional description has recently required modification because it has been shown that (*a*) T_{mG} varies with changes in G.F.R. and extracellular fluid volume (see reviews by Kurtzman & Pillay, 1973; Morel & de Rouffignac, 1973), (*b*) glucose can be reabsorbed in sites other than the proximal convoluted tubule (von Baeyer, 1975; Bishop, Green & Thomas, 1976; Bishop & Green, 1979*a*, *b*).

The well described glycosuria of pregnancy in humans has been postulated to be due to either an increased filtered load of glucose (Christiansen, 1958) or to a decreased T_{mG} (Welsh & Sims, 1960); and it might be presumed that similar mechanisms are operative in the rat. These postulates, however, were arrived at on the basis of the conventional model and, as indicated above, this is not adequate to explain more recent findings. In fact, the present data give the first direct evidence that neither of these mechanisms is responsible for the increased glucose excretion by the pregnant rat.

The amount of glucose reabsorbed by the proximal tubule was greater in pregnant animals than in virgin controls at both normal and elevated plasma glucose levels and while it might be argued that this does not, of itself, constitute an *increased* T_{mG} in pregnant animals, there is certainly no indication of a reduction. Therefore, impairment of T_{mG} cannot explain the increased glucose loss, particularly at normal plasma concentrations (Bishop & Green, 1980) where the filtered load of glucose is much lower than the maximum that the tubule can absorb (compare the amount of glucose absorbed during glucose infusion with filtered load during saline infusion (Tables 1, 2).

The amount of glucose filtered was higher in pregnant animals than virgin controls during saline infusion, but again this cannot be construed as a major contributory factor to the increased glucose loss since the amount of glucose leaving the proximal tubule was no higher in pregnant animals than virgins; and, indeed, during glucose infusion it was very much less.

If the proximal tubule cannot be implicated as the main determinant of the increased glucose loss, the impairment must be in reabsorptive processes in the loop of Henle, distal tubule and collecting ducts where 5–8 % of the glucose is normally reabsorbed. There is evidence that the loop of Henle (von Baeyer, 1975; Bishop *et al.* 1976; Bishop & Green, 1979*b*) and the collecting duct (Bishop & Green, 1979*a*) normally reabsorb glucose; and preliminary evidence suggests that reabsorption in both sites is impaired during pregnancy (Bishop & Green, 1979*a*, *b*).

The mechanisms whereby glucose is reabsorbed when plasma glucose is normal, involve reabsorption of glucose to a limiting low glucose concentration in proximal tubular fluid (Rohde & Deetjen, 1968; Bishop *et al.* 1979). At higher plasma glucose concentrations, there appear to be other mechanisms operative in that glucose is reabsorbed in a concentration similar to that in the tubular fluid (Loeschke,

Baumann, Renschler & Ullrich, 1969; Stolte *et al.* 1972; Knight, Senekjian, Sansom & Weinman, 1980): i.e. tubular fluid glucose concentrations are similar to those in plasma ($TF/P_{glucose} = 1$). Solvent drag has been postulated as being important under these circumstances (Stolte *et al.* 1972) as have other passive mechanisms (Loeschke *et al.* 1969), although Knight *et al.* (1980) concluded from their results that active reabsorption of glucose was also increased. While our results in virgin animals confirm the previous findings, the demonstration of a $TF/P_{glucose}$ of 0·68 at high plasma glucose concentrations in pregnant animals suggests that active glucose reabsorption is stimulated; such increased active transport of glucose in pregnant animals is in contrast to previous suggestions (Welsh & Sims, 1960) of a decrease. Alternatively, the data might indicate that different mechanisms for glucose reabsorption were operative in pregnant animals.

Sodium and fluid

Although increased sodium and water reabsorption have been described during saline (Lichton, 1963; Lichton & Hugh, 1968; Katz & Lindheimer, 1973; Atherton & Pirie, 1977; Bishop & Green, 1980) and glucose infusion (Bishop & Green, 1980) during pregnancy in the rat, the stage of pregnancy at which these increases become apparent differs in different experimental series. Davison & Lindheimer (1980) were unable to find an increase in 9- to 10-day pregnant rats, and attributed this to using conscious instead of anaesthetized animals; but Atherton (1981) has presented evidence to the contrary and showed that the increased sodium and fluid reabsorption were greater in conscious animals when compared with anaesthetized at this stage.

In the present experiments, significantly increased absolute fluid and sodium reabsorption in the proximal tubule was only found in those animals which had an increased S.N.G.F.R. (pregnant animals during saline infusion); yet fractional reabsorption of water and sodium (see Fig. 5) was similar in all series; i.e. the reabsorption of fluid matched the filtered load whether the animals were pregnant or not and irrespective of the nature of the infusion. The mechanisms involved in this maintenance of glomerulo-tubular balance are not known, but it is interesting to speculate that in the saline loaded pregnant animals the increased tubular flow rate of itself may account for the differences in reabsorption (see Green, Moriarty & Giebisch, 1981). Thus, changes in fractional reabsorption of sodium and water that have been described for the whole kidney in pregnancy (e.g. Atherton & Pirie, 1977; Bishop & Green, 1980) are unlikely to be due to increased fractional reabsorption per unit proximal tubular length; but may be related to the increased length of the proximal tubule found in pregnancy (Garland *et al.* 1978) or to changes in segments of nephron beyond the proximal tubule.

In summary, we have demonstrated that increased loss of glucose in the urine of pregnant rats cannot be attributed, exclusively or even primarily, to alteration of proximal tubular function or to increased filtered load, at least not in the superficial nephrons; and is most easily explained by altered glucose reabsorption by segments beyond the end of the proximal tubule. It is possible that reabsorption of water and ions is also altered in these later segments of nephron. In the absence of direct evidence from humans, it is tempting to postulate that similar considerations apply and that neither of the theories for pregnancy glycosuria (Christiansen, 1958; Welsh & Sims, 1960) is valid.

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