

EFFECTS OF PREGNANCY ON GLUCOSE HANDLING BY RAT KIDNEYS

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SUMMARY

1. Glomerular filtration rate (g.f.r.), and renal reabsorption and excretion of glucose, sodium and potassium were measured in 7–8 day pregnant rats and age-matched (12–13 week old) virgin controls undergoing saline and glucose infusions.

2. Pregnancy was associated with an increased g.f.r. and a decreased urine flow rate during both infusions.

3. During saline infusion, more glucose was excreted in pregnant animals than in virgins but with no significant difference in fractional reabsorption. During glucose infusion, pregnant animals excreted less glucose than virgins, owing to a decrease in the filtered load but with no significant difference in fractional reabsorption.

4. During both saline and glucose infusion, pregnant animals excreted less sodium than virgin controls.

5. During saline infusion, pregnant animals excreted more potassium. During glucose infusion, pregnant animals excreted less potassium than control animals.

INTRODUCTION

Pregnancy is associated with major changes in renal function. These have been best documented in human studies and include an increase in glomerular filtration rate (g.f.r.; see Hytten & Leitch, 1971, for review; Davison & Hytten, 1974); an increase in salt and water reabsorption (Hytten & Leitch, 1971); and a tendency to excrete increased amounts of glucose in the urine even when this has not been detected clinically as frank glycosuria (Davison & Hytten, 1975). The mechanisms underlying these changes are obscure, largely because appropriate investigations cannot be performed in humans.

The rat has been used extensively for investigating renal function in non-pregnant animals. For the pregnant rat, some similarities with human pregnancy have been demonstrated at a whole kidney level in that g.f.r. is increased (Matthews & Taylor, 1959; Lindheimer & Katz, 1971; Atherton & Pirie, 1977) and there is increased salt and water reabsorption (Lichten, 1963; Lichten & Hugh, 1968; Katz & Lindheimer, 1973; Atherton & Pirie, 1977). While it has been demonstrated that rats normally have some glucose in the urine (see Bishop, Elegbe, Green & Thomas, 1978, for references), it is not known whether pregnancy influences the amount that is excreted.

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The current study was therefore designed to investigate whether pregnant rats had a defect in glucose handling similar to that described for humans. If such a defect were present, then it might be possible to use the pregnant rat in an attempt to gain some insight into the mechanisms underlying the increased glucose excretion in pregnancy. Renal excretion of glucose was investigated during saline infusion, where glucose losses were small, and during glucose infusion, where the reabsorptive capacity of the tubules was exceeded and frank glycosuria occurred in both pregnant animals and virgin controls.

METHODS

Experiments were performed on female Sprague-Dawley rats all aged 12–13 weeks, prepared as described previously (Bishop *et al.* 1978). Briefly, animals were anaesthetized by an intra-peritoneal injection of 100 mg.kg⁻¹ body weight of Inactin (5-ethyl-5-[1'-methyl-propyl]-2-thiobarbiturate) and placed on a thermostatically controlled operating table set to maintain body temperature at 38 °C. Catheters were inserted into the left jugular vein for administration of fluids; and into the right carotid artery for recording systemic blood pressure (via a Statham P23 Dc transducer and a Grass P7 polygraph). Tracheostomy ensured a clear airway. The bladder was catheterized suprapubically taking care to reduce dead space to a minimum and to occlude the urethra.

Saline (150 m-mole.l⁻¹) was administered intravenously as a priming dose (0.8 ml. containing [³H]inulin 16 μCi.ml.⁻¹) to compensate for fluid losses occurring during surgery, and as a continuous sustaining infusion (200 μl.min⁻¹ containing 5 μCi.ml.⁻¹ [³H]inulin). After 4 hr the infusion was changed to 5% D-glucose (200 μl.min⁻¹ with the same concentration of inulin) which was continued for a further 3 hr. The first 1.5 hr of the saline infusion was allowed for induction and steady maintenance of a saline diuresis; thereafter, urine samples were collected for half-hour periods in pre-weighed glass vials containing a little liquid paraffin to prevent evaporation. At half-hourly intervals, blood samples were obtained from a tail vein, collected in pre-heparinized microhaematocrit tubes and then centrifuged to give plasma samples.

Experiments were performed in two groups of animals; eight virgin controls and ten 7–8 day pregnant animals. The length of pregnancy was estimated from the appearance of a cervical plug of mucus on the floor of the cage after mating. Pregnancy was confirmed after completion of the experiment.

Analyses

[³H]inulin was counted in 10 μl. samples of urine or plasma, in a liquid scintillation counter (Intertechnique SL30), using P.C.S. (Amersham-Searle, Illinois, U.S.A.) diluted 1:1 with A.R. toluene as scintillant. Sodium and potassium concentrations were measured in suitably diluted samples by flame photometry. Glucose was analysed using a modification of the hexokinase method (see Bishop *et al.* 1978), the fluorescence being measured on a fluorocolorimeter (Aminco, Silver Springs, Md., U.S.A.).

Calculations

$$\begin{aligned} \text{Glomerular filtration rate} &= C_{\text{in}} = (U_{\text{in}} \cdot V) / P_{\text{in}} \\ \text{Filtered load of substance X} &= C_{\text{in}} \cdot P_{\text{X}} \\ \text{Reabsorbed load} &= (C_{\text{in}} \cdot P_{\text{X}}) - (U_{\text{X}} \cdot V) \\ \text{Fractional reabsorption} &= [(C_{\text{in}} \cdot P_{\text{X}}) - (U_{\text{X}} \cdot V)] / (C_{\text{in}} \cdot P_{\text{X}}) \end{aligned}$$

where C_{in} is the clearance, P_{in} the plasma concentration and U_{in} the urinary concentration, of inulin; V is the urine flow rate and U_{X} and P_{X} are the concentrations of any substance X in urine and plasma respectively.

Statistics

Results are presented in Figs. 1–7 as mean \pm s.e. of mean for each collection period. The statistical significance of differences between pregnant and virgin animals during saline and glucose infusion was assessed using analysis of variance (Snedecor & Cochran, 1967), excluding

the half-hour period immediately following the change of infusion where gross changes occurred but most variables were not in steady state. Time zero is the time after 1.5 hr of saline infusion when steady-state excretion had been attained (see Results).

RESULTS

The mean arterial blood pressure was not significantly different between virgin and pregnant rats and remained above 100 mmHg (13 kPa) in every case. Pregnant animals were heavier than virgin animals by 10–15 %, as has been described previously (Garland, Green & Moriarty, 1978); but the difference in wet weight of the kidneys (1.70 ± 0.12 g for virgin; 1.99 ± 0.11 g for pregnant) was not statistically significant ($0.1 > P > 0.05$).

Plasma concentrations of sodium and potassium (Fig. 1) were dependent on the type of infusion, plasma sodium being significantly lower during glucose infusion ($P < 0.001$) as was plasma potassium ($P < 0.01$) than during saline infusion. While pregnancy was not associated, under these conditions, with any significant differences in plasma sodium, the plasma potassium in pregnant animals was lower ($P < 0.05$) than in virgins except during the half-hour period immediately succeeding the change to glucose infusion. In both virgin and pregnant animals, there was a marked rise in plasma glucose when glucose was infused; the rise in plasma glucose was much greater in virgin than in pregnant animals ($P < 0.001$). During saline infusion there were no significant differences in plasma glucose between pregnant and virgin animals.

Values for outputs of constituents in the urine and for amounts reabsorbed by the kidney have not been normalized for differences in body weight or kidney size, for several reasons. Multiple factors are probably involved in the renal changes in pregnancy and it is not possible to determine from the present data whether these are dependent on alteration in kidney size or in body weight. As argued by others (see Hytten & Leitch, 1971), a more important relationship may be between the renal handling and the number of nephrons, and the latter is not significantly altered in pregnancy in the rat (Balmer, Garland, Green, Moriarty & Richardson, 1977). Accordingly the raw data are presented.

Urine flow rate (Fig. 2) was significantly less in pregnant animals, regardless of the type of infusion ($P < 0.05$) although the difference was greater during saline infusion; the type of infusion had no significant effect on flow rate in either the pregnant or virgin animals. Pregnant rats retained more of the infused fluid, but these changes cannot be attributed to changes in g.f.r. (Fig. 2) since pregnant animals had a higher g.f.r. than virgins ($P < 0.001$); this confirms work by Atherton & Pirie (1977). The differences in g.f.r. were more marked during saline infusion than during glucose infusion; however, there were no statistically significant differences in g.f.r. between glucose and saline infusion in either the virgin or the pregnant rat.

Glucose (Fig. 3)

During saline infusion, pregnant animals consistently excreted more glucose, at a higher concentration, than virgin controls. This was associated with a slightly greater filtered load ($P < 0.01$) accounted for by a higher g.f.r. (Fig. 2) with a similar glucose concentration (Fig. 1). There was a significant increase in the absolute reabsorption of glucose ($P < 0.01$) but no difference in fractional reabsorption (Fig. 3).

During glucose infusion, however, pregnant animals excreted much less glucose than controls and at a lower urinary concentration. This was associated with a reduced filtered glucose load in pregnant animals (Fig. 3), accounted for mainly by a reduced plasma glucose level. The absolute reabsorption of glucose was decreased in pregnant animals when compared with virgin controls although fractional glucose reabsorption did not differ between the two series.

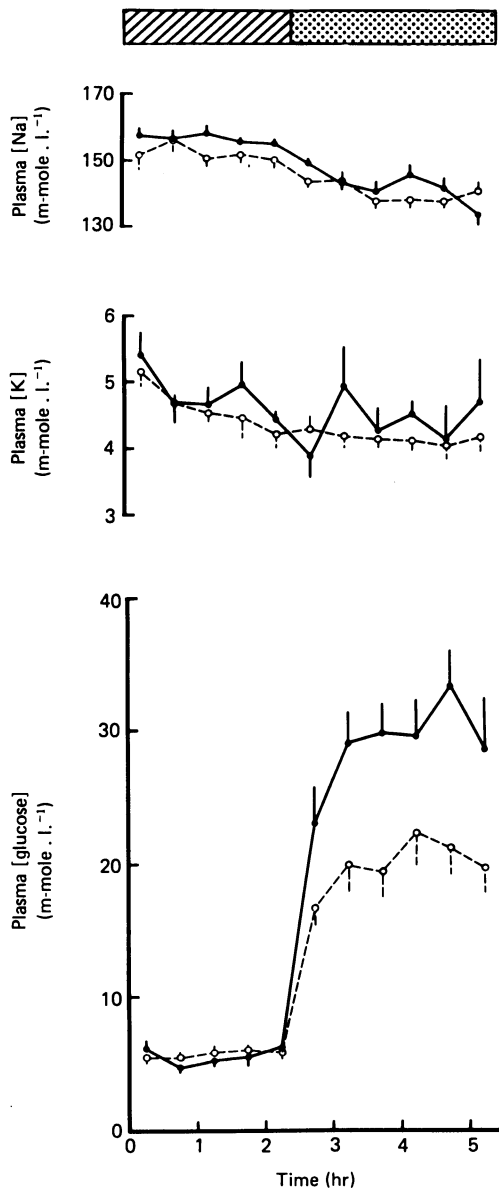


Fig. 1. Plasma concentration of sodium, potassium and glucose during saline infusion (shown by the cross-hatched bar) and glucose infusion (shown by the stippled bar). Continuous lines represent virgin control and dashed lines pregnant animals. Error bars are ± 1 S.E. of mean.

When glucose infusion was compared with saline infusion, there was, in both pregnant and virgin animals, a significant increase in plasma glucose (Fig. 1), glucose excretion, urinary concentration, filtered load and absolute reabsorption, but a decrease in fractional reabsorption (Fig. 3).

Sodium (Fig. 4)

There were no significant differences in urinary sodium concentration between virgin and pregnant animals during either saline or glucose infusion, although during glucose infusion there was significantly less sodium excreted than during saline

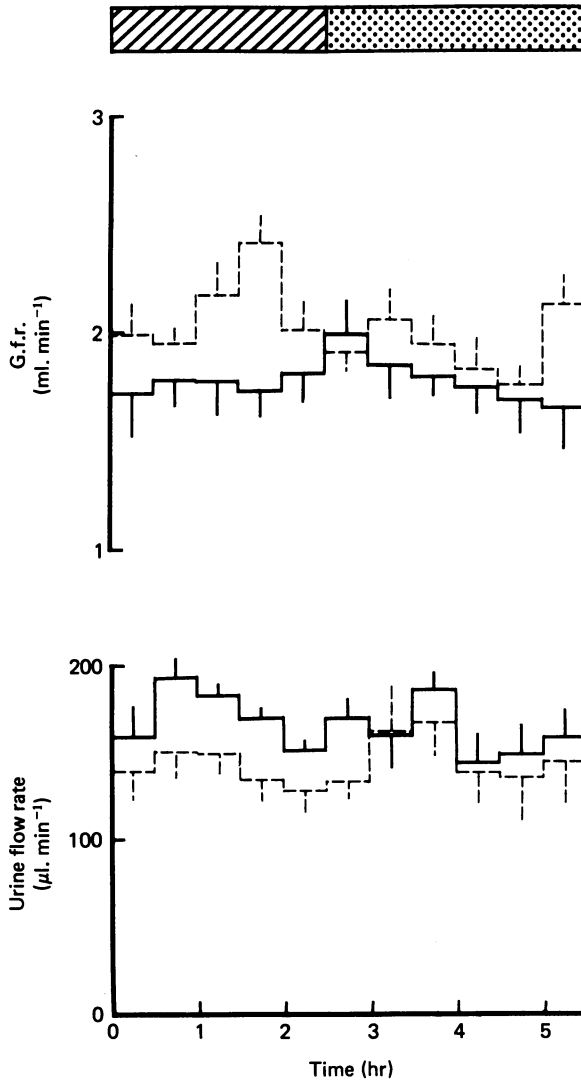


Fig. 2. Glomerular filtration rate and urine flow rates in anaesthetized rats. The hatched bar indicates the period during which saline was infused and the stippled bar the period over which glucose was infused. Continuous lines indicate virgin controls and dashed lines pregnant animals. Error bars are ± 1 s.e. of mean.

infusion in both pregnant and virgin animals ($P < 0.001$). The difference in sodium excretion between virgin and pregnant animals, during both saline and glucose infusion ($P < 0.001$), is a reflexion of the changes in urinary flow rate. More sodium was filtered by pregnant animals (plasma sodium similar but g.f.r. increased) and more was reabsorbed (in both absolute and fractional terms; $P < 0.001$). The infusate did not have a substantial effect on the absolute amount of sodium reabsorbed; it was only slightly, though significantly, reduced during glucose infusion ($P < 0.05$). There was, however, a substantial increase in fractional reabsorption during glucose infusion in both virgin and pregnant animals. Throughout both infusions, pregnant animals reabsorbed a greater proportion of the sodium filtered than the virgin controls ($P \ll 0.001$).

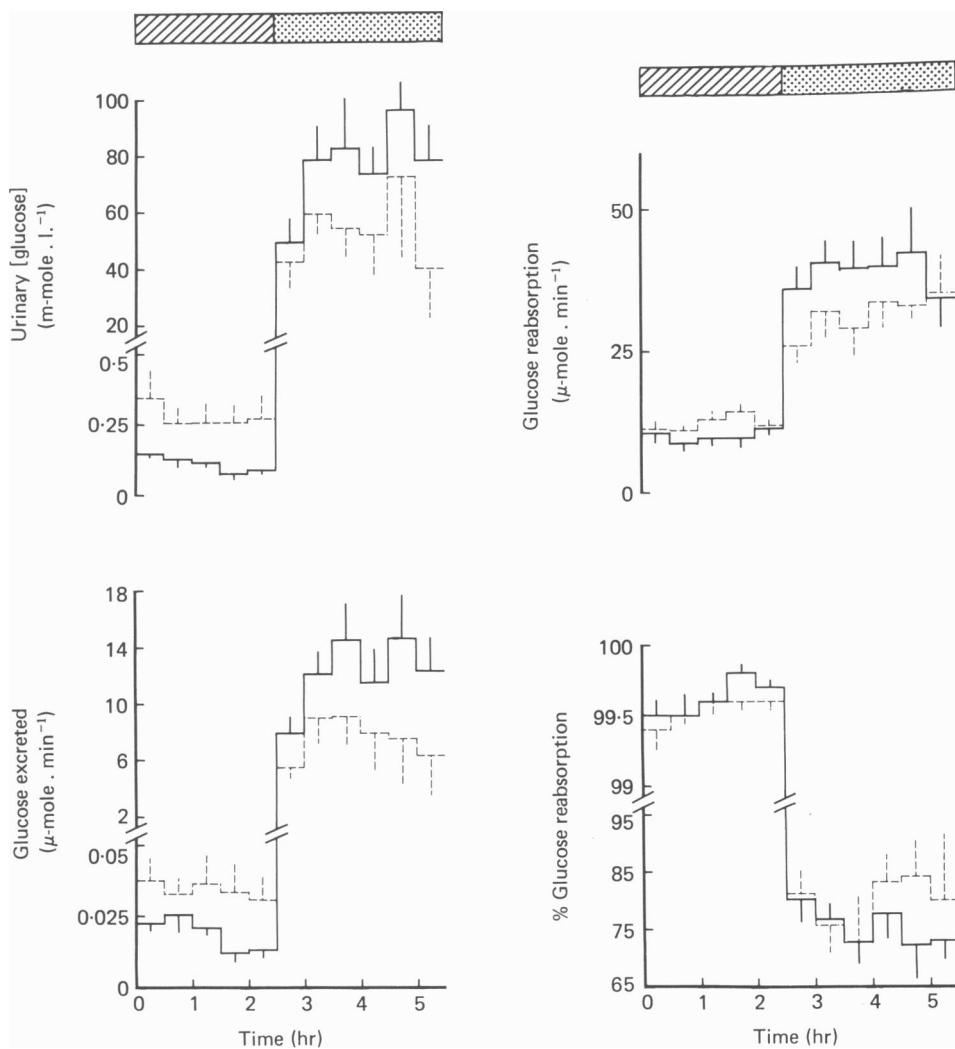


Fig. 3. Amount and concentration of glucose, excreted in the urine, and absolute and fractional reabsorption of glucose during saline infusion (shown by cross-hatched bars) and glucose infusion (shown by stippled bars). Continuous lines represent virgin controls and dashed lines pregnant animals. Error bars are ± 1 s.e. of mean.

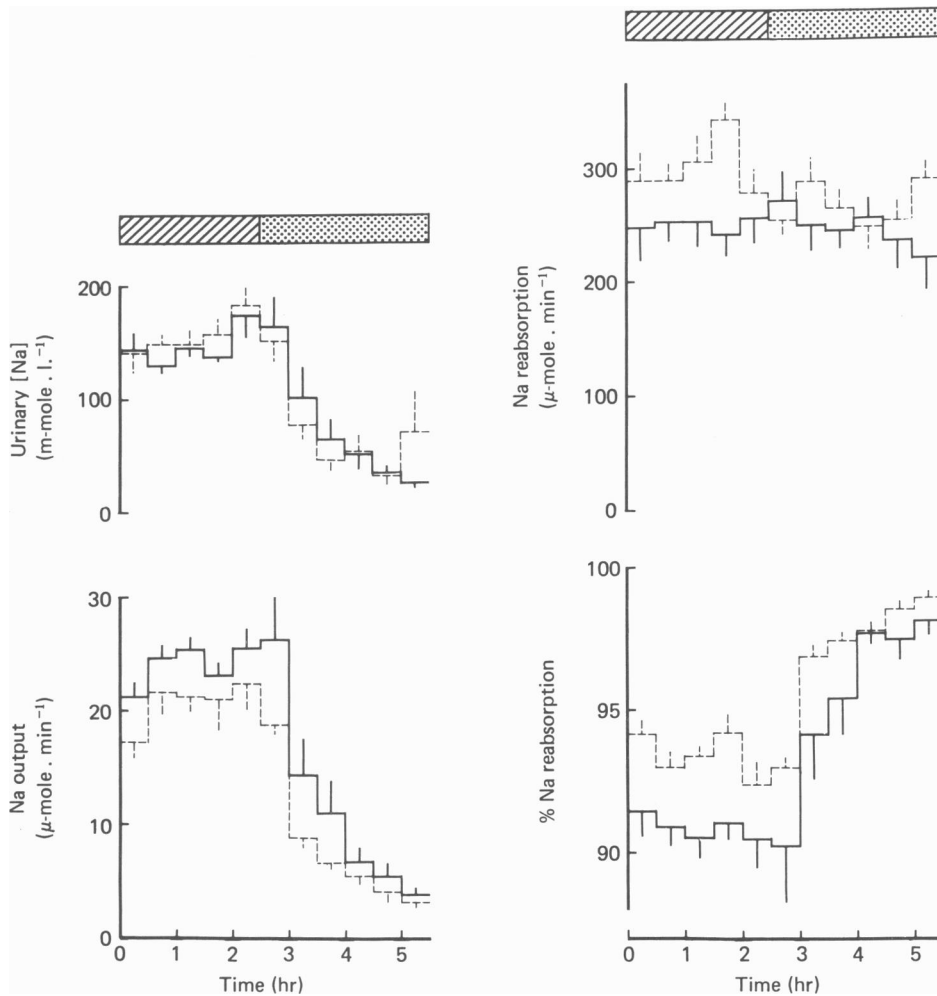


Fig. 4. Amount and concentration of sodium excreted in the urine and absolute and fractional reabsorption of sodium during saline infusion (shown by cross-hatched bars) and glucose infusion (shown by stippled bars). Continuous lines represent virgin controls and dashed lines pregnant animals. Error bars are ± 1 s.e. of mean.

Potassium (Fig. 5)

During saline infusion, pregnant animals had significantly higher urinary potassium concentration and excretion than virgin controls ($P < 0.01$). Since this was associated with no significant difference in *absolute* potassium reabsorption, there was a significant decrease in *fractional* potassium reabsorption ($P < 0.01$). During glucose infusion, both the excretion and the urinary concentration of potassium decreased, particularly in pregnant animals, so that the mean urinary potassium concentration was not different from the virgin controls. The amount excreted was now significantly less than controls, however ($P < 0.01$).

Glucose infusion was not associated with any change in absolute potassium reabsorption for either virgin or pregnant animals but under these circumstances the fractional reabsorption was greater in pregnant animals ($P < 0.01$).

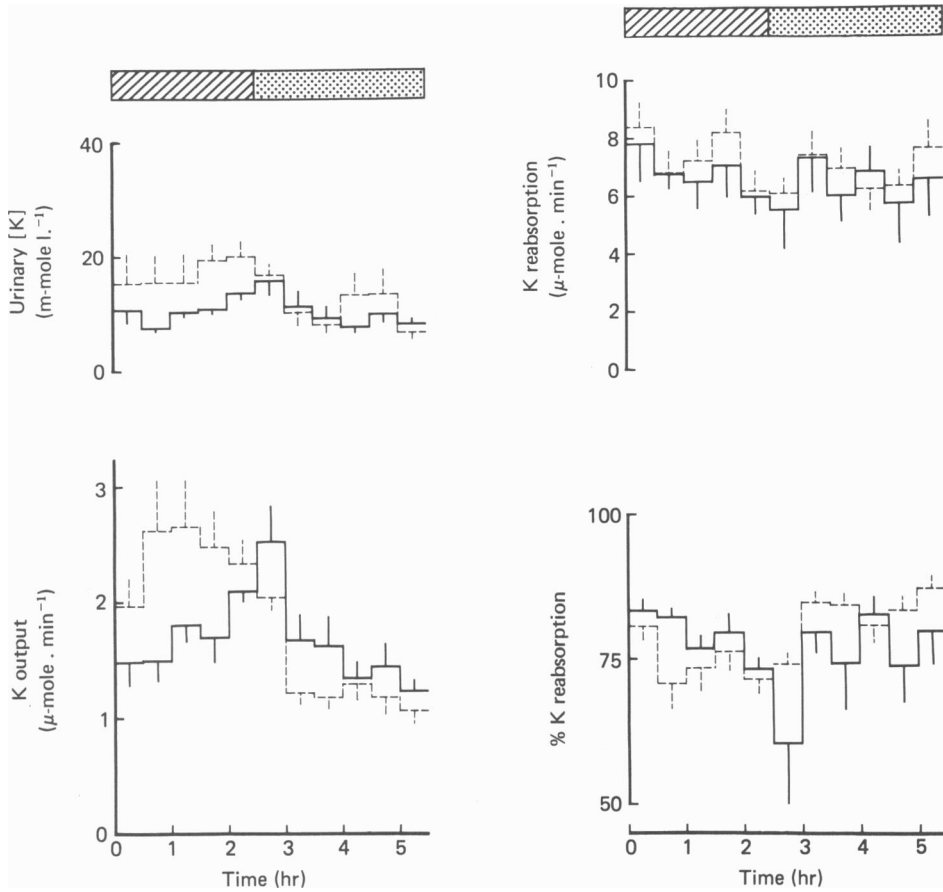


Fig. 5. Amount and concentration of potassium excreted in the urine and absolute and fractional reabsorption of potassium during saline infusion (shown by cross-hatched bars) and glucose infusion (shown by stippled bars). Continuous lines represent virgin controls and dashed lines pregnant animals. Error bars are ± 1 S.E. of mean.

DISCUSSION

The main findings in the present study are: first, that in confirmation of previous work (see Introduction), pregnancy was associated with decreased urine flow, increased g.f.r. and altered sodium excretion; secondly, that during saline infusion at normal plasma glucose levels, excretion of glucose was greater in pregnant animals; thirdly, that during glucose infusion as performed in the present experiments, excretion of glucose was, paradoxically, lower in pregnant animals; and fourthly, that there was no significant correlation between sodium, potassium and glucose handling by the kidney.

These experiments were not designed to investigate the mechanisms underlying the decreased urine flow rate nor the increased g.f.r. The effect of pregnancy on the latter has recently been investigated in Munich-Wistar rats and the increased g.f.r. attributed to an increased renal plasma flow (Baylis, 1980).

Sodium

The increased absolute and fractional reabsorption and the reduced excretion of sodium found both during saline or during glucose infusion are consistent with previous results from animals undergoing saline diuresis at similar (Atherton & Pirie, 1977) and later stages of pregnancy (Lichton, 1963; Lichton & Hugh, 1968). Katz & Lindheimer (1973) and Davison & Lindheimer (1980), however, were unable to demonstrate such results in early pregnancy but suggested that the difference might be explained by their use of conscious animals.

Although information about the nephron site and the mechanisms responsible for the increased reabsorption of sodium must await more detailed data about proximal and distal tubular function, some of the pertinent facts are (a) that proximal convoluted tubules increase in length early in pregnancy (Garland *et al.* 1978); (b) that reabsorption rate per mm length of proximal tubule is unaltered (H. O. Garland, personal communication); and (c) that aldosterone levels are raised during pregnancy (Landau & Lugibihl, 1961; Watanabe, Meeker, Grey, Sims & Solomon, 1963).

Glucose

The conventional description of glucose handling by the mammalian kidney is of active proximal tubular reabsorption of glucose up to a constant maximum transport rate (Tm_G) which, at normal plasma glucose concentrations, sufficiently exceeds the filtered load to permit excretion of glucose-free urine (Smith, 1951). On this basis, increased glucose excretion in human pregnancy has been postulated to be the consequence of either an increased filtered load (Welsh & Sims, 1960) or a decreased Tm_G (Christiansen, 1958). The conventional description of glucose handling has recently required modification, however, in that: (a) Tm_G is not constant, but varies with changes in g.f.r. and extracellular fluid volume (see reviews by Kurtzman & Pillay, 1973; Morel & deRouffignac, 1973) and (b) glucose can be reabsorbed at sites other than the proximal convoluted tubule (von Baeyer, 1975; Bishop, Green & Thomas, 1976; Bishop & Green, 1979*a, b*). Because the mechanisms underlying glucose reabsorption are not fully understood, it is difficult to say what the nature of the change is in pregnancy.

During saline infusion the filtered load of glucose was greater in pregnant animals than in virgins, and in spite of increased reabsorption more glucose was excreted in the urine. These changes could be either secondary effects of the changes in fluid volume and g.f.r. that occur in pregnancy or direct effects of some factor (e.g. a hormone associated with pregnancy) on nephron transport. In addition changes may not solely represent altered *proximal* tubular reabsorption. It should be noted that an increased g.f.r., as occurs in pregnant animals (see Fig. 2), would be expected to increase Tm_G (see Morel & deRouffignac, 1973; Kurtzman & Pillay, 1973) while the increased extracellular fluid volume occurring in pregnancy (Pirie, 1979) might be expected to decrease Tm_G (see Morel & deRouffignac, 1973; Kurtzman & Pillay, 1973). Preliminary results have also indicated that glucose handling in the loops of Henle (Bishop & Green, 1979*b*) and in distal parts of the nephron (Bishop & Green, 1979*a*) is altered in pregnant rats. Therefore, although the fact of increased glucose excretion at normal plasma glucose in pregnant animals is clearly established by the

present study, more sophisticated experiments are necessary to clarify the causal mechanisms.

Interpretation of the data from the experiments at high plasma glucose concentrations is even more difficult. The reduced reabsorption of glucose by pregnant animals, when compared with virgin controls, is probably a consequence of a lowered filtered load which, in turn, is mainly due to a lower plasma glucose concentration (Fig. 3). Superimposed on this are the effects of increased g.f.r. and increased extracellular volume (see above), the latter being exaggerated during the glucose infusion because of retention of salt and water during the preceding saline infusion (Fig. 4). In an attempt to minimize this problem of saline retention, infusion of glucose at this high infusion rate ($200 \mu\text{l. min}^{-1}$) without prior infusion of saline was attempted; but in contrast to findings when the infusion of glucose was $100 \mu\text{l. min}^{-1}$ (Bishop *et al.* 1978; Bishop & Green, 1979a), the condition of the animals (particularly renal function) rapidly deteriorated and the attempt was abandoned. The lower flow rates used previously (Bishop *et al.* 1978; Bishop & Green, 1979a) did not produce consistent frank glycosuria. Because there are so many factors affecting glucose reabsorption in these animals during glucose infusion in pregnancy, it is impossible to infer if the underlying reabsorptive mechanisms have been altered.

Relations between sodium, potassium and glucose

It has been suggested previously that glucose reabsorption by the kidney increased the reabsorption of sodium and water (Kurtzman, White, Rogers & Flynn, 1972). Bishop *et al.* (1978) were unable to confirm this conclusion and further work on proximal tubular reabsorption in rats strengthened their contention that there was little effect, quantitatively, of glucose reabsorption on sodium reabsorption (Bishop *et al.* 1978, 1979). Similarly, the current experiments provide no support for direct coupling of sodium reabsorption to glucose reabsorption since, when glucose reabsorption was increased (during glucose infusion in both pregnant and virgin animals), there were no significant differences in sodium reabsorption (see Figs. 3 and 4). This lack of relationship was apparent in individual experiments as well as in the mean data.

Glucose entry into many cells is known to be associated with uptake of potassium (Crone, 1966). Although potassium excretion and glucose excretion were both increased in pregnant animals during saline infusion (Figs. 3 and 5), there was no significant difference in reabsorption of potassium between pregnant and virgin animals nor between the two infusion solutions, even though the amount of glucose reabsorbed was markedly altered, showing that there is no consistent relationship between glucose and potassium reabsorption.

Although the increased potassium excretion during saline infusion in pregnant animals is accompanied by increased reabsorption of sodium, and so might be related to the increased plasma levels of aldosterone (Landau & Lugibihl, 1961; Watanabe *et al.* 1963), this explanation is unlikely to account for the changes during glucose infusion in pregnant animals, when increased fractional reabsorption of potassium occurs with increased sodium reabsorption. There must be other factors involved.

In summary, the pregnant rat can be a useful model of human pregnancy in that we and others have demonstrated similar changes: viz. altered g.f.r. and salt and water handling. To these findings can now be added altered glucose handling, at least when plasma glucose concentrations were normal.

The current data confirm the main purpose of these experiments: to provide a basis for more detailed micropuncture experiments in order to investigate the mechanisms which underlie the altered renal function. Preliminary results indicate that pregnant rats have impaired glucose reabsorption in the loop of Henle and the collecting duct (Bishop & Green, 1979*a, b*).

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