Pregnancy Restores the Renal Vasodilator Response to Glycine in Dahl Salt-Sensitive Rats

Shirley A. Whitescarver, Cheryl M. Heesch

To determine if pregnancy alters the impaired renal vasodilator responses in hypertensive Dahl salt-sensitive (Dahl S) rats, we measured glomerular filtration rate and effective renal plasma flow and calculated renal vascular resistance before, during, and after renal vasodilation with glycine (0.17 mmol/kg per minute IV). Conscious, midterm (day 11 to 14) pregnant and age-matched virgin Dahl S and Dahl salt-resistant (Dahl R) rats were fed an 8% NaCl diet for 4 weeks (n=6 per group). Mean arterial pressure was elevated (P<.05) in Dahl S compared with Dahl R rats, with no significant difference between pregnant and virgin animals in either group. Pregnancy resulted in significant increases in plasma volume, baseline glomerular filtration rate, and renal plasma flow and a significant decrease in renal vascular resistance. The glycine-induced increase in filtration rate in virgin Dahl S rats (27±4%) was less (P<.01) than pregnant Dahl S (60±4%) and either group of Dahl R (virgin, 43±3%; pregnant, 45±5%) rats. Similarly, the 21±4% increase in renal plasma flow in virgin Dahl S rats was less (P<.01) than the pregnant Dahl S (45±4%) and either pregnant (45±5%) or virgin (45±5%) Dahl R rats. Glycine decreased renal vascular resistance only 12±2% in the virgin Dahl S compared with 31±3% in the pregnant Dahl S rats and 30±4% and 28±3% in pregnant and virgin Dahl R rats. In summary, the impaired renal vasodilator response in Dahl S rats is restored by pregnancy.

KEY WORDS • hypertension, renovascular • glomerular filtration rate • vascular resistance • vasodilation • hemodynamics • glycine

Homer Smith and colleagues were the first to observe that glomerular filtration rate (GFR) increased in conscious dogs when they were switched from a cracker meal diet to a meat diet. In 1944, Robert Pitts demonstrated that intravenous administration of the amino acid glycine duplicated the increase in GFR and effective renal plasma flow (ERPF) after a high-protein meal and that these increases were due to a fall in total renal vascular resistance (RVR). This capacity of normal kidneys to increase GFR and ERPF in response to a high-protein intake suggests a renal vasodilator reserve.

The increase in renal function after ingestion of protein or an intravenous amino acid load has been used to assess the residual vasodilator capacity or renal reserve in both humans and animals. In addition, it has been used to identify the presence of hyperfiltration in humans. Some but not all reports suggest that a blunted renal vasodilator response to an amino acid infusion or high-protein diet may be indicative of compromised or diseased kidneys.

Chronic hyperfiltration due to glomerular disease or loss of renal mass was believed to lead to glomerular damage. However, during normal pregnancy there is a chronic hyperfiltration and hyperemia in both humans and rats that is not associated with glomerular damage, and closely spaced multiple pregnancies have no harmful effect on kidney function in rats with two normal kidneys. It is now believed that chronically elevated glomerular blood pressure, rather than elevated filtration, is responsible for glomerular damage.

In the rat, the maximum gestational increase in both GFR and ERPF occurs during midterm pregnancy. Baylis reported that, despite significantly elevated baseline GFR and ERPF in midterm pregnant Munich-Wistar rats, the response to a glycine infusion was similar to that observed in virgin control rats (approximately 30% increase in GFR and ERPF). Less is known about the effect of pregnancy on renal function in hypertensive animals. Although the time course is different, spontaneously hypertensive rats (SHR), like mildly hypertensive women, have a decrease in arterial pressure during gestation. Examining the effects of pregnancy on renal function in SHR, Baylis found that midterm pregnant SHR did not exhibit pregnancy-induced renal vasodilation and both pregnant and virgin SHR were refractory to the renal vasodilator effects of glycine. The refractoriness to glycine and the lack of pregnancy-induced renal vasodilation both suggest that structural adaptations as a result of the hypertension could be a contributing factor.

Another rat model of hypertension, the Dahl salt-sensitive (Dahl S) rat, also has an impaired ability to

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vasodilate in response to an amino acid load. Tobian et al\(^1\) reported that, unlike Dahl salt-resistant (Dahl R) rats, the renal vasculature of Dahl S rats has an impaired ability to vasodilate in response to a mixed amino acid infusion, even before the development of hypertension. Research has focused on the role of the kidney in the development of hypertension in the Dahl S rat.\(^1\) Although there is no abnormality in baseline GFR in Dahl S rats, abnormalities in the ability of the kidneys to vasodilate in response to decreased perfusion pressure\(^2\) and a high-salt diet\(^3\) have been reported. Thus, it appears that under a variety of circumstances the kidneys of Dahl S rats do not vasodilate appropriately.

The effects of pregnancy on blood pressure and renal function in the Dahl S model of hypertension are not known. Because the lack of renal vasodilation in response to a high-salt diet in Dahl S rats has been proposed to contribute to the hypertension in this model, it was of interest to evaluate the blood pressure and renal response to pregnancy. In the present study, renal vasodilator capacity was assessed in both virgin and midterm pregnant Dahl S and Dahl R rats maintained on a high-salt diet.

**Methods**

Experiments were performed in 12 female Dahl S and 12 female Dahl R rats of the Brookhaven strain obtained from Harlan Sprague Dawley Inc, Indianapolis, Ind. Both midterm pregnant (days 11 to 14) and age-matched virgin controls were studied. For mating, female rats were placed in a cage with a male rat in the evening. The next morning vaginal smears were obtained. If sperm were present, this was designated as day 1 of pregnancy. All rats were maintained on a high-salt diet. Experiments were performed in 12 female Dahl S and 12 female Dahl R rats of the Brookhaven strain obtained from Harlan Sprague Dawley Inc, Indianapolis, Ind. Both midterm pregnant (days 11 to 14) and age-matched virgin controls were studied. For mating, female rats were placed in a cage with a male rat in the evening. The next morning vaginal smears were obtained. If sperm were present, this was designated as day 1 of pregnancy. All rats were maintained on a high-salt diet and arterial pressure was recorded with Halothane volatile anesthesia, and femoral artery, jugular vein, and bladder catheters were implanted.

On the day of the experiment, rats were anesthetized with Halothane volatile anesthesia, and femoral artery, jugular vein, and bladder catheters were implanted. Vascular catheters were exteriorized between the scapulae. The bladder catheter was a modification of the chronic bladder catheter of Gellai and Valtin.\(^2\) After surgery, a lidocaine paste was applied to all incision sites, and animals were placed in a specially designed adjustable rat restrainer that allows forward and backward movement. Arterial pressure was recorded throughout the experiment with a low-compliance Statham pressure transducer (P23Db) connected to a Grass polygraph (model 7D). Animals were allowed to recover for at least 3 hours before renal measurements were begun. Studies were conducted according to National Institutes of Health and The Ohio State University guidelines for animal care.

Plasma volume and hematocrit were measured in conscious animals before infusions. Plasma volume was determined by the dye dilution method with Evan’s blue dye (T-1824, Sigma Chemical Co, St Louis, Mo). Briefly, 200 µL of 0.6% Evan’s blue dye was injected into the jugular vein catheter and flushed with 200 µL of isotonic saline. Ten minutes later, a 200-µL blood sample was taken from an ear vein. Standards were made from serial dilutions of the 0.6% stock solution. The concentration of dye was determined with a Turner spectrophotometer (optical density, 620 nm) and plasma volume calculated from the standard curve.

Renal function in conscious animals was measured before, during, and after renal vasodilation with an intravenous infusion of glycine. Inulin (5%, Pfannstiel Laboratories, Inc, Waukegan, Ill) and 0.4% para-aminomhippuric acid (PAH; Merck Sharp & Dohme, West Point, Pa) in Ringer’s solution were infused at a rate of 10 µL/min per 100 g body wt. At least 60 minutes was allowed for equilibration of inulin and PAH. Furthermore, urine collections were not begun until urine output matched the infusion rate so that the animals were in fluid equilibrium before the study. Two 15-minute urine samples were collected for the determination of baseline renal function (control period). Renal vasodilator capacity or renal reserve was assessed by addition of glycine (15 g/100 mL solution) to the inulin/PAH infusion. The glycine infusion (0.17 mmol/kg per minute) was infused for 1 hour, and two 15-minute urine samples were collected during the last 30 minutes (glycine period). The single amino acid glycine was used because other researchers have demonstrated that its renal vasodilator effects are not due to expansion of extracellular fluid volume or hyperosmolarity.\(^5\) The control inulin/PAH solution was again infused for 1 hour, and two 15-minute urine collections were made during the last 30 minutes for the recovery period. Thus, 30 minutes was allowed for equilibration before both the glycine period and recovery period urine collections.

GFR and ERPF were measured by the clearance of inulin and PAH. Urine volumes of all samples were determined gravimetrically. A 200-µL blood sample was obtained at the midpoint of the control, glycine, and recovery periods for determination of plasma concentrations of inulin and PAH. Urine and plasma inulin and PAH concentrations were determined colorimetrically by the methods of Führ et al\(^2\) and Waugh and Beall.\(^2\) Filtration fraction (FF) was calculated as GFR/ERPF. Effective renal blood flow (ERBF) was calculated as ERPF/(1−Hct), where Hct is hematocrit. Renal venous pressure (RVP) was estimated as 5 mm Hg. RVR was calculated as (MAP−RVP)/ERBF, where MAP is mean arterial pressure.

**Statistical Analysis**

Data are expressed as mean±SEM. A three-way analysis of variance (ANOVA) with repeated measures was used to compare GFR, ERPF, FF, RVR, and MAP between groups. A two-way ANOVA was used for all other comparisons. The Newman-Keuls multiple-range test was used for determination of statistical significance, with a value of P≤.05 considered significant.

**Results**

Body weight was higher in the pregnant animals, and there was no difference between the Dahl S and Dahl R rats (Table). Wet kidney weights were not different between Dahl S and Dahl R rats in either the pregnant (Dahl S, 2.72±0.09 g; Dahl R, 2.64±0.12 g) or virgin (Dahl S, 2.41±0.11 g; Dahl R, 2.51±0.09 g) groups. However, when values from all pregnant rats were compared with those from virgin rats, pregnant animals had significantly higher wet kidney weights (pregnant, 2.68±0.07 g; virgin, 2.46±0.07 g, P<.05).
Response to Gfycine

There was no difference in the average days of pregnancy (Dahl S, 12.8±0.3 days; Dahl R, 13.2±0.3 days) or number of fetuses in utero (Dahl S, 13.0±0.5; Dahl R, 13.5±0.9) at the time of the study.

MAP was higher in the virgin Dahl S compared with virgin Dahl R rats but was not significantly different between pregnant Dahl S and pregnant Dahl R rats (Table). Although pregnancy tended to decrease MAP in Dahl S rats, there was no significant difference between pregnant and virgin animals in either group. Hematocrit values were higher in virgin Dahl S compared with virgin Dahl R rats, and pregnancy decreased hematocrit by the same degree in both groups. This significant decrease in hematocrit reflects a gestational plasma volume expansion in both rat strains. Measurement of plasma volume confirmed the volume expansion between pregnant and virgin animals in either the Dahl S (virgin, 13.5±0.9) at the time of the study.

MAP indicates mean arterial pressure; Hct, hematocrit; and PV, plasma volume. Values are mean±SEM for midterm pregnant (days 11 to 14) and virgin Dahl salt-resistant and Dahl salt-sensitive rats fed an 8% NaCl diet for 4 weeks.

There was no significant difference in the average days of pregnancy (Dahl S, 12.8±0.3 days; Dahl R, 13.2±0.3 days) or number of fetuses in utero (Dahl S, 13.0±0.5; Dahl R, 13.5±0.9) at the time of the study.

MAP was higher in the virgin Dahl S compared with virgin Dahl R rats but was not significantly different between pregnant Dahl S and pregnant Dahl R rats (Table). Although pregnancy tended to decrease MAP in Dahl S rats, there was no significant difference between pregnant and virgin animals in either group. Hematocrit values were higher in virgin Dahl S compared with virgin Dahl R rats, and pregnancy decreased hematocrit by the same degree in both groups. This significant decrease in hematocrit reflects a gestational plasma volume expansion in both rat strains. Measurement of plasma volume confirmed the volume expansion. Both total plasma volume and plasma volume per 100 g body weight were higher in the pregnant compared with virgin animals (Table).

Control Period

There was no significant difference in GFR between the virgin Dahl R (1.58±0.06 mL/min) and Dahl S (1.59±0.21 mL/min). Pregnancy increased GFR in both the Dahl R (1.84±0.08 mL/min, P<0.01) and Dahl S (1.76±0.19 mL/min, P<0.05) rats (Fig 1). ERPF was higher (P<0.01) in the virgin Dahl R (4.56±0.14 mL/min) compared with the virgin Dahl S (3.87±0.18 mL/min) rats. Similar to GFR, midterm pregnant rats had higher (P<0.01) ERPF compared with virgin rats during the control period. ERPF in pregnant Dahl R rats averaged 5.27±0.24 mL/min, which was higher (P<0.01) than in pregnant Dahl S animals (4.46±0.38 mL/min; Fig 2). Taken as a group, Dahl S animals had higher (P<0.05) baseline FF values compared with Dahl R rats. There was no difference in FF between virgin and pregnant animals in either the Dahl S (virgin, 0.41±0.04; pregnant, 0.41±0.04) or Dahl R (virgin, 0.35±0.02; pregnant, 0.35±0.02) groups. Baseline RVR was higher (P<0.01) in virgin Dahl S rats (22.66±2.12 mm Hg/[mL/min]) compared with virgin Dahl R rats (16.19±0.71 mm Hg/[mL/min]). Pregnancy decreased RVR significantly in both Dahl S (19.91±2.68 mm Hg/[mL/min]) and Dahl R (14.47±0.98 mm Hg/[mL/min]) rats (Fig 3).

Response to Glycine

Arterial pressure was unaltered by the glycine infusion. During the glycine infusion MAP was 119±4 mm Hg in the pregnant and 121±3 mm Hg in the virgin Dahl R rats. These values were not significantly different from the control values reported in the Table. During the glycine infusion, MAP values in the pregnant (143±9 mm Hg) and virgin (160±15 mm Hg) Dahl S rats were also not different from the control period.

GFR increased significantly in response to glycine in all the groups; however, the percent increase was significantly less in the virgin Dahl S rats (27±4%) compared with pregnant Dahl S (60±4%) or either group of Dahl R (virgin, 43±3%; pregnant, 45±5%) rats (Fig 1). Although absolute values during glycine infusion were higher in the pregnant compared with virgin Dahl R rats, the percent increase from control was not significantly different. In contrast, in addition to the higher absolute values, there was also a significant difference in the percent increase from control GFR values in pregnant compared with virgin Dahl S rats. The 27% increase in the Dahl S virgin rats was lower (P<0.01) than all other groups, and the 60% increase in the pregnant Dahl S rats was higher (P<0.01) than all other groups. Thus, in Dahl S rats, pregnancy potentiated...
Glycine-induced hyperfiltration above that observed in normotensive Dahl R rats.

Glycine significantly increased ERPF in all groups, but similar to GFR, the increase was significantly less in the virgin Dahl S rats (Fig 2). Absolute values during the glycine period were higher in the pregnant compared with the virgin Dahl R rats such that the percent increase in ERPF in response to glycine was 45% in each group. The 21±4% increase in ERPF in the virgin Dahl S rats during glycine infusion was significantly lower than in the pregnant Dahl S rats (45±4%), which was not significantly different from either group of Dahl R rats (virgin, 45±5%; pregnant, 45±5%). Thus, pregnancy restored the hyperemic response to glycine in Dahl S rats. If only rat strain was considered in the statistical comparison, glycine resulted in an increase (P<.05) in FF in Dahl S (0.41±0.03 to 0.44±0.03) but not Dahl R (0.35±0.01 to 0.34±0.01) rats. However, there was no difference in the increase between the virgin (0.41±0.04 to 0.43±0.05) and pregnant (0.41±0.04 to 0.44±0.04) Dahl S animals. FF was unaltered by the glycine infusion in the Dahl R rats (virgin, 0.35±0.02 to 0.35±0.03; pregnant, 0.35±0.02 to 0.34±0.02).

Glycine infusion resulted in a significant decrease in RVR in all four groups. However, the decrease in virgin Dahl S rats (12±2%) was significantly less than in pregnant Dahl S (31±3%) and either pregnant (30±4%) or virgin (28±3%) Dahl R rats (Fig 3).

Recovery Period

There were no significant differences in MAP, GFR, or ERPF between the control and recovery periods in any group. The only difference between the control and recovery periods was in RVR in the virgin Dahl S rats, which had a higher (P<.05) value during the recovery period. These results indicate that the renal vasodilation was due to glycine, was reversible, and was not an effect of time.

Discussion

The results of the current study clearly demonstrate that pregnancy alters the renal vasodilator response to an intravenous glycine infusion in hypertensive Dahl S rats. Compared with virgin Dahl R rats, virgin Dahl S rats had an impaired ability to increase both GFR and ERPF in response to a glycine load. These results are similar to those reported by Tobian et al in prehypertensive male Dahl rats. In that study, anesthetized Dahl S rats increased GFR only 18% to a mixed amino acid infusion compared with an 81% increase in the Dahl R rats. Although conscious female Dahl S rats increased GFR and ERPF significantly in the present study, the percent increase was significantly less than that seen in the Dahl R rats. In contrast, pregnant Dahl S rats had no impairment in their ability to increase either GFR or ERBF. Although the increase in ERPF in the pregnant Dahl S rats was equal to both groups of Dahl R rats, the hyperfiltration was significantly greater than in the Dahl R rats and may reflect some structural differences between the strains.

The effects of pregnancy on renal vasodilator capacity in normotensive Dahl R rats are very similar to results in normotensive Munich-Wistar rats reported by Baylis. Anesthetized Munich-Wistar rats responded to a comparable glycine load with approximately a 30% increase in both GFR and ERPF. The increase in the conscious Dahl R rats was approximately 45% in both GFR and ERPF. Unlike the reports in SHR, the hypertensive, virgin Dahl S rats did vasodilate in response to a glycine load. However, this response was impaired compared with the normotensive Dahl R rats. Also, unlike the SHR, this impairment was reversed in the pregnant Dahl S rats. MAP was not significantly different between virgin and midterm pregnant Dahl S rats. Thus, it appears that the impairment was not due...
to structural adaptations that occur as a result of the hypertension.

Renal function in this study was evaluated in conscious rats at least 3 hours after recovery from volatile anesthesia and surgery. Arterial pressure in virgin Dahl R rats was 122±3 mm Hg during the control and 114±3 mm Hg during the recovery periods. Arterial pressures of 111±2 mm Hg have been reported in chronically instrumented, unrestrained Dahl R rats 5 days after surgery. Therefore, it is likely that the higher blood pressure in the current study was due to acute surgical stress. However, GFR and ERPF values were similar to those reported in chronically instrumented normotensive rats allowed 5 days of recovery.

Other researchers have reported pregnancy-induced increases in GFR and ERPF in both anesthetized and chronically instrumented midterm pregnant normotensive rats. Despite the difference in protocols, we also observed a midgestational increase in both GFR and ERPF in both the Dahl S and Dahl R rats. Thus, unlike another hypertensive model, the SHR, hypotensive Dahl S rats did exhibit gestational renal vasodilation.

Pregnancy results in a decrease in arterial pressure in both humans and rats. There was a tendency for arterial pressure to be lower in the gravid animals in the present study, but the difference did not achieve significance. In SHR, the decrease in arterial pressure is more pronounced at term. For the determination of arterial pressure followed throughout pregnancy.

Hematocrit and plasma volume measurements indicated a gestational volume expansion in both the Dahl S and Dahl R rats. In studies with pregnant Munich-Wistar rats, Baylis has reported a significant increase in plasma volume as early as day 6. Measurements in other normotensive strains and SHR demonstrate that rats have a significant increase in plasma volume by midterm pregnancy. In the current study we cannot rule out increased plasma volume as a contributing factor to the gestation-induced renal hyperfiltration. However, Reckelhoff et al demonstrated that expanding plasma volume to a level equivalent to that reported for midterm pregnant rats did not alter single nephron filtration rate in the virgin rat.

The glycine-induced increases in GFR and ERPF cannot be attributed to changes in arterial pressure, because there was no significant difference in pressure during the three periods in any group. These results are similar to other studies that have reported no alteration in arterial pressure with comparable infusions of glycine. These studies have also demonstrated that the increases in GFR and ERPF are not due to an osmotic effect of glycine, because equimolar infusion of dextrose has no effect on GFR and ERPF in the rat.

The vasodilator effect of amino acids on renal hemodynamics is well characterized, but the mechanism remains controversial. Many possible mediators, such as glucagon and prostaglandins or alterations in tubuloglomerular feedback, have been proposed. Although nitric oxide has not been proved to be the primary mediator of amino acid-induced hyperfiltration, several recent studies have suggested that endothelium-derived nitric oxide may be important to this response. Tolins and Raij first demonstrated that blockade of nitric oxide synthesis with the competitive inhibitor N\textsuperscript{\textsubscript{6}}-monomethyl L-arginine (L-NMMA) inhibited the renal hyperfiltration and hyperemia induced by a mixed amino acid infusion.

Endothelium-derived nitric oxide is synthesized from a nitrogen atom in the guanidino group of the amino acid L-arginine. In the present study we used the amino acid glycine. Although glycine is not a nitrogen donor source for the formation of nitric oxide, it is a metabolizable amino acid, and metabolizable amino acids other than L-arginine have been shown to induce renal vasodilation in isolated perfused kidneys.

King et al studied the role of nitric oxide in glycine-induced renal vasodilation. Their study compared the inhibitory effect of L-NMMA on hyperfiltration and hyperemia induced by infusion of either mixed amino acids or the single amino acid glycine. L-NMMA caused a modest blunting of the mixed amino acid-induced hyperfiltration but failed to curtail the renal hyperemia. Lack of blockade of the renal hyperemia was attributed to L-arginine in the mixed amino acid infusion. In contrast, blockade of nitric oxide synthesis with L-NMMA completely blocked the renal hyperemic response and attenuated the glycine-induced hyperfiltration. Thus, the glycine-induced hyperfiltration is only partly dependent on nitric oxide. In fact, Wang et al have reported that the dopamine subtype 1 receptor agonist fenoldopam abolishes the glycine-induced hyperfiltration without altering the hyperemia.

Recent reports indicate that part of the mechanism of hypertension in the Dahl S rat may be the inability to increase nitric oxide levels with increased salt intake. A recent study by Chen and Sanders in the Dahl/Rapp salt-sensitive rat supports this hypothesis. Not only did an intravenous bolus dose of L-arginine acutely lower pressure, but the development of hypertension could actually be prevented with daily L-arginine treatment. Thus, the attenuated response to the glycine infusion in the virgin Dahl S rats fed a high-salt diet may be due to decreased levels of nitric oxide. With the recent reports that endothelium-derived nitric oxide is increased during pregnancy, it is possible that the restoration of the glycine-induced hyperfiltration and hyperemia due to increased nitric oxide formation in the pregnant Dahl S rats. Furthermore, if pregnancy increases nitric oxide, this may be why the Dahl S rat exhibits pregnancy-induced renal vasodilation. Thus, the difference between the renal vasodilator response of the SHR and Dahl S rat to both pregnancy and glycine may be related to the salt dependence and therefore the role of nitric oxide in the development of hypertension.

In summary, similar to male Dahl S rats, virgin female Dahl S rats have an impaired ability to vasodilate in response to a glycine load. However, the renal vasodilator response in midterm pregnant Dahl S rats was similar to Dahl R rats. Thus, pregnancy restores the renal vasodilator response to glycine in hypertensive Dahl S rats.

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