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The Antihypertensive Effect of Pregnancy in Spontaneously Hypertensive Rats (39471)

W. AOI, D. GABLE, R. E. CLEARY, P. C. M. YOUNG, AND M. H. WEINBERGER

Specialized Center of Research in Hypertension, and the Departments of Medicine and Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, Indiana 46202

In the normal rat, blood pressure has been observed to decline during the last week of pregnancy (1, 2). Studies in humans (3) and dogs (4) have shown that pregnancy is accompanied by increased sodium needs, presumably related to natriuretic factors in pregnancy (3). Normal pregnant rats demonstrate a preference for salt that is evident early in pregnancy and maintained until delivery (5). Thus increased sodium needs and a decline in blood pressure appear to be associated with normal pregnancy in several species.

The blood pressure lowering effect of pregnancy can also be observed in rats made hypertensive by renal artery constriction with and without contralateral nephrectomy (6) or by wrapping the kidney in cellophane (perinephritis) (7). However, not all forms of experimental hypertension are ameliorated by pregnancy, since studies have reported no change in blood pressure during pregnancy in rats with desoxycorticosterone acetate (DOCA)-salt hypertension and unilateral nephrectomy (8, 9).

The spontaneously hypertensive rat (SHR) developed by Okamoto and Aoki (10) has been extensively studied as a model of idiopathic hypertension. The present study was designed to examine the effects of pregnancy on blood pressure in the SHR in comparison to similar observations in rats of the Kyoto-Wistar (KW) strain.

Methods. Twenty-two female SHR and 24 female KW rats, 8 to 10 months of age, (Cox Laboratory Supply Company) were studied. All rats were given free access to standard rat chow (Purina Company) and tap water. Half of the animals were used as nonpregnant controls. All females were mated with male rats of the same strain after vaginal smears indicated estrus. Males were caged with females for 2 nights and then removed following which the females were caged individually.

Systolic blood pressure was measured in the morning by a tail-cuff method (11). The rats were placed in an incubator at 37°C for 15 min and then placed in an adjustable container and the tail seated onto the plethysmograph. Three readings were averaged for each individual blood pressure determination. Pregnant animals were studied through delivery and for 2 days postpartum. Nonpregnant controls were studied throughout the same time period. Statistical analyses were performed by t test (12).

Results. Figure 1 shows systolic blood pressure in the nonpregnant SHR (n = 12) and normotensive KW rats (n = 12). As can be seen in the figure, blood pressure of nonpregnant SHR was significantly ($P < 0.001$) higher than that of nonpregnant KW rats.

Figure 2 similarly demonstrates systolic blood pressure in the pregnant SHR (n = 10) and pregnant KW (n = 12) rats. The pregnant SHR had significantly ($P < 0.005$) higher average systolic blood pressure than did pregnant KW rats during the initial 19 days of gestation, but demonstrated a marked decline in blood pressure from an average maximum of 201 ± 18 (SD) mm Hg to an average minimum of 123 ± 20 mm Hg during the 5 days before delivery. No significant difference in blood pressure was seen between the two groups on the day prior to delivery. The blood pressure in the pregnant KW rats was significantly lower ($P < 0.005$) on the delivery day, 113 ± 9 mm Hg than that in

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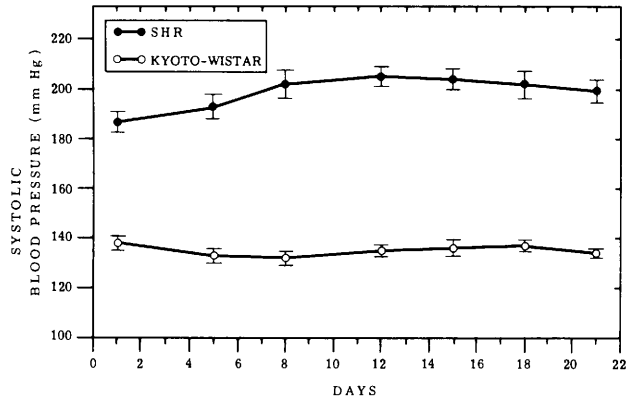

FIG. 1. Mean systolic blood pressure (± 1 standard error) in nonpregnant Kyoto-Wistar (open circles, n = 12), and SHR (closed circles, n = 12).

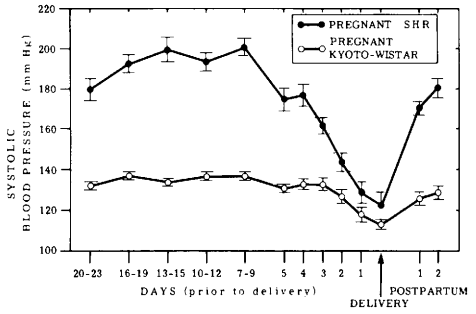

FIG. 2. Mean systolic blood pressure (± 1 standard error) in pregnant Kyoto-Wistar (open circles, n = 12), and SHR (closed circles, n = 10). The day of delivery is indicated by the arrow.

nonpregnant KW rats, 134 ± 6 mm Hg. Two days after delivery, blood pressure in pregnant SHR and KW rats again rose to an average level of 181 ± 5 and 129 ± 3 mm Hg, respectively.

Discussion. Although the SHR has been extensively studied as a model of spontaneous hypertension, the mechanisms for the development and maintenance of hypertension remain unclear. In the present study, the physiologic changes induced by pregnancy were associated with a marked decline in blood pressure to normal in the SHR during the last 3 days of gestation. Qualitatively similar changes in blood pressure were seen in the normotensive Kyoto-Wistar control rats. The mediation of these changes may be important in our understanding of the hypertension in the SHR.

The amelioration of hypertension by pregnancy is not unique to the SHR. Other forms of experimental hypertension in rats, induced by renal artery constriction (6) or by bilateral renal encapsulation (7), have demonstrated marked decreases in blood pressure during pregnancy. However, not all forms of experimental hypertension are improved by pregnancy. Two studies (8, 9) have failed to observe a decrease in blood pressure in the animal made hypertensive by administration of DOCA and salt during pregnancy. The latter observations would imply that in the DOCA-salt model of experimental hypertension the natriuretic effects of pregnancy are not sufficient to reduce blood pressure. This may not necessarily be the case however, since it is recognized that the DOCA-salt model may have a hypertensive component unrelated to the acute effects of mineralocorticoid administration (meta-corticoid or post-DOCA hypertension) which persists after cessation of the steroid.

While the present study was restricted to observations of blood pressure, several possible mechanisms for the antihypertensive effect of pregnancy in the SHR can be speculated upon. Pregnancy is associated with a variety of humoral and hemodynamic changes. One example is the increased production of progesterone. Progesterone is known to be an antagonist of mineralocorticoid activity and thus a natriuretic factor. It has been reported that peak increases in plasma progesterone and its production rate occur between the 15th and 20th days of normal murine pregnancy (13, 14). It is curious that this is precisely the time when blood pressure began to

decline in the pregnant SHR of the present study. However, similar changes would be anticipated in the pregnant control rats. Since it has been reported that the nonpregnant SHR has significantly lower plasma aldosterone levels than Kyoto-Wistar rats (15), it is conceivable that comparable levels of circulating progesterone could have exerted a relatively greater natriuretic effect in the pregnant SHR. Thus it is possible that the marked decline in blood pressure observed in pregnant SHR may have been due to a relatively greater change in extracellular fluid volume or a greater sensitivity to changes in volume than in the pregnant normotensive rats.

It is also known that pregnancy is associated with increased production of prostaglandins, kinins, and other humoral factors thought to influence sodium and/or water metabolism. It is possible that the pregnant SHR, for unknown reasons, may be more sensitive to such factors. Indeed others have speculated upon the role of prostaglandins in abnormalities of blood pressure control during pregnancy (16). The observations of the present study do not permit precise identification of the factor(s) responsible for the marked decline of blood pressure in the pregnant SHR. A variety of mechanisms are possible. It has been demonstrated that pregnant animals and humans have greater sodium needs than their nonpregnant counterparts (3, 4). This is apparently due to a natriuretic effect of pregnancy (3). If this effect is sufficient to cause extracellular volume depletion, a reduction in blood pressure could ensue. Further studies of sodium and fluid dynamics are necessary to define whether such factors are responsible for the dramatic decrease in blood pressure in pregnant SHR observed in the present study. Alternatively, other factors may be involved in this phenomenon. Further investigation of the mechanisms responsible for the observations of the present study may help clarify the etiology and pathophysiology of hypertension in the SHR.

Summary. Pregnancy in the SHR is associated with a marked and significant decline in blood pressure into the normal range before delivery. While a mild decrease in blood pressure was also seen during the last 3 days of gestation in the normotensive pregnant rats, the mechanism for the marked change in blood pressure in the SHR is not clear. Further investigation of the blood pressure effects of pregnancy in the SHR may improve our understanding of the pathophysiology involved in this model of experimental hypertension.

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