

Effect of an Oral Contraceptive Agent on Blood Pressure Response to Renin (34640)

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An occasional patient develops hypertension that appears to be related to the use of oral contraceptive agents (1). There is suggestive evidence linking changes in the renin-angiotensin-aldosterone system to the change in blood pressure. Renin, an enzyme from the kidney, acts on renin substrate, a plasma protein, to release angiotensin, a powerful vasoconstrictor and stimulator of aldosterone secretion. The concentration of renin-substrate is increased by estrogens, and was increased in all patients studied by Laragh with hypertension apparently produced by oral contraceptives (2).

Renin substrate has not been considered to be rate-limiting *in vivo* (3). We have found that rats treated with large amounts of an oral contraceptive had a decreased blood pressure response to angiotensin but an increased blood pressure response to renin, suggesting that renin substrate was rate-limiting *in vivo*.

Materials and Methods. Twenty Holtzman albino female rats, weighing 200 to 250 g, were treated with norethynodrel with mestranol (Enovid R), given orally in their diet, in amounts calculated to give the normal human amount of a weight basis (0.01 mg/kg/day). Twenty additional rats received 10× the normal human amount of Enovid (1.0 mg/kg/day) and 20 untreated rats served as control animals.

After 3 weeks on therapy the rats were anesthetized with 30 mg/kg of sodium pentobarbital and the femoral artery and external jugular vein were cannulated. The blood pressure response to 0.12, 0.25, and 0.50 μ g/kg angiotensin (Ciba) was then determined on 10 animals randomly selected from each group.

The blood pressure response to renin was determined on the 10 remaining animals from

each group. The renin was prepared by a modification of the method of Haas and Goldblatt (3). Amounts that gave a blood pressure response approximately equal to the 3 dose levels of angiotensin were used. The blood pressure was recorded continuously on a Grass polygraph recorder. The renin and angiotensin were given intravenously.

Results. Figure 1A shows the blood pressure response to angiotensin. The rats which received 1.0 mg/kg/day Enovid (10× normal dose) had a significant ($p < 0.01$) decrease in their blood pressure response to the largest amount of angiotensin given. There was no significant difference in angiotensin responsiveness between the control group and the animals which received the normal dose (0.1 mg/kg/day) of Enovid.

Figure 1B shows the blood pressure response to renin. A completely different pattern of response is now evident. There was a significant ($p < 0.01$) increase in blood pressure response to all doses of renin in the rats treated with 1.0 mg/kg/day Enovid (10× normal dose). The animals which received the normal dose of Enovid appeared to have a decreased blood pressure response to renin but the differences were not significant.

Discussion. The changes produced by estrogens and progestational agents are complex and may have opposing influences on vascular and electrolyte homeostasis. Estrogen may cause sodium retention directly by action on the kidney, and indirectly by increasing venous volume (4, 5). Progestational agents are said to cause sodium excretion (6). Estrogens increase renin-substrate (3), and the progestogen, norethynodrel, increases aldosterone secretion (7). This study demonstrates that angiotensin responsiveness is decreased, as it is in many conditions

where renin is increased.

The complexity of the changes produced by oral contraceptives makes it difficult to state the precise cause of the hypertension occasionally found in association with their use. Two conclusions can be drawn from the studies reported here. First, renin substrate is apparently rate-limiting *in vivo* in the blood pressure response to exogenous renin, thus confirming the suggestion of Laragh (2). Secondly, measurement of renin levels may not give a true guide to angiotensin production. Also, as angiotensin responsiveness can be

reduced by oral contraceptive agents, determination of both angiotensin levels and angiotensin responsiveness is necessary before the role of changes in the renin-angiotensin system in the genesis of oral contraceptive-produced hypertension can be evaluated.

It is probable that the changes in renin responsiveness found in this study would be present with any oral contraceptive containing estrogens and progestins. Similar studies with agents containing only progestins are planned.

Summary. Rats were treated with norethyn-

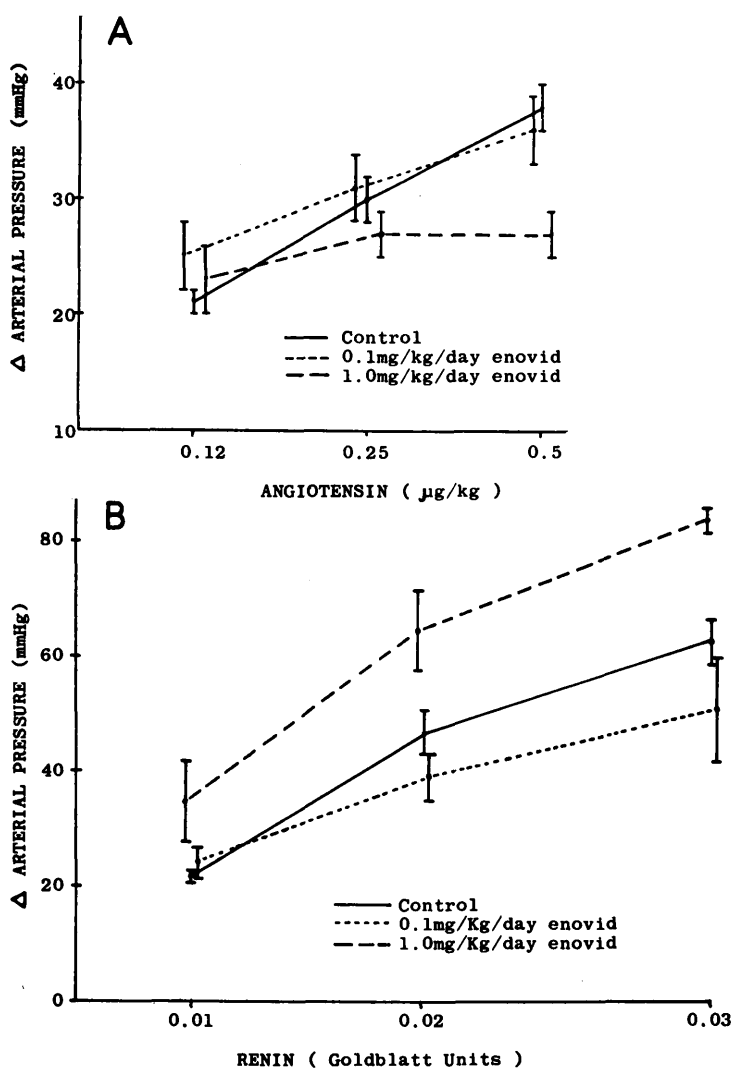


FIG. 1. The effect of chronic Enovid administration on the blood pressure response to angiotensin (A), and renin (B) is shown. Standard errors of the mean are indicated.

odrel with mestranol given orally mixed with their diet in amounts calculated to give 1 and 10× the normal human amount on a weight basis. The animals which received 10× normal norethynodrel-mestranol had a significant decrease in their blood pressure response to the largest amount of angiotensin and a significant increase in their blood pressure response to renin. These data indicate that renin substrate is rate-limiting *in vivo*.

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1. Newton, M., Sealey, J., and Ledingham, J., *Amer. J. Obstet. Gynecol.* **101**, 1037 (1968).
2. Laragh, J., Sealey, J., Ledingham, J., and Newton, M., *J. Amer. Med. Ass.* **201**, 918 (1967).
3. Haas, E., and Goldblatt, H., *Circ. Res.* **20**, 45 (1967).
4. Dignam, W. S., Voskian, J., and Assali, N. S., *J. Clin. Endocrinol.* **16**, Metab. 1032 (1956).
5. Ueland, K., and Parer, J., *Amer. J. Obstet. Gynecol.* **96**, 400 (1966).
6. Katz, F., and Kappas, A., *J. Clin. Invest.* **46**, 1768 (1967).
7. Laidlaw, J. C., Ruse, J. L., and Gornall, A. G., *J. Clin. Endocrinol. Metab.* **22**, 161 (1962).

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