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Does Renin Play a Rôle in the Maintenance of Normal Blood Pressure?*

GEORGE E. WAKERLIN AND GEORGE R. CHOBOT.

From the Department of Physiology, College of Medicine, University of Illinois.

Research during the past few years points strongly to the probability that the Goldblatt[1] type of experimental renal hypertension results from the liberation by the constricted kidney of some effective substance which directly or indirectly acts as a pressor agent.[2-7] As a consequence, interest in the pressor substance, renin, which was first extracted from the kidney by Tigerstedt and Bergmann[8] has been revived.

Although there is scant, circumstantial evidence that renin is involved in the pathogenesis of experimental renal hypertension,[9, 10] no evidence is available at present for the possibility that renin plays a rôle in the maintenance of normal arterial blood pressure. We have investigated the latter possibility by determining (1) the renin content of the kidneys and the blood pressures of normal dogs, (2) the effect of splanchnic stimulation, and (3) the effect of induced hypotension on the renin content of the kidneys of normal dogs. Splanchnic stimulation and hypotension constitute conditions of physiological stress which conceivably might affect the formation and secretion of renin.

Two methods of preparing renin were used. One consisted of extracting the ground kidney with 0.2% HCl in physiological salt solution, centrifuging, storing overnight in the ice box, and recentri-

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1 Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W., *J. Exp. Med.*, 1934, **59**, 347.

2 Page, I. H., *Am. J. Physiol.*, 1935, **112**, 166.

3 Elaut, L., *Comp. rend. Soc. biol.*, 1936, **122**, 126.

4 Goldblatt, H., Gross, J., and Hanzal, R. F., *J. Exp. Med.*, 1937, **65**, 233.

5 Freeman, N. E., and Page, I. H., *Am. Heart J.*, 1937, **14**, 405.

6 Child, C. G., and Glenn, F., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 217.

7 Alpert, L. K., Alving, A. S., and Grimson, K. S., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 1.

8 Tigerstedt, R., and Bergmann, P. G., *Skand. Arch. Physiol.*, 1898, **8**, 223.

9 Harrison, T. R., Blalock, A., and Mason, M. F., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 38.

10 Prinzmetal, M., and Friedman, B., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 122.

fuging. The other method was that of Grossman[11] which involved extracting alcohol-ether desiccated kidney pulp with 0.5% $NaHCO_3$ in physiological salt solution.

The renin extracts were assayed by mean blood pressure determinations from the cannulated femoral artery of the dog, using a standard intravenous dose of 0.5 g of kidney equivalent per kg of assay animal. Successive injections were made at half-hour intervals in order to avoid cumulative pressor effects as far as possible. Contrary to the findings of Pickering and Prinzmetal,[12] we have found no significant difference in the response to renin of unanesthetized dogs and dogs anesthetized with sodium barbital. We have, however, found that bilateral nephrectomy performed one to 3 hours previously definitely increases the dog's reactivity to renin. Thus, whereas only one-third of 30 non-nephrectomized dogs, equally divided between anesthetized and unanesthetized animals, proved to be satisfactory assay subjects, two-thirds of 60 dogs nephrectomized one to 3 hours previously were satisfactory. Moreover, the reactivity to renin before and after bilateral nephrectomy was studied in a group of 10 dogs. Each animal showed an increased response following removal of the kidneys. This is in accord with the report of an increased pressor response to renin obtained in dogs nephrectomized 2 to 3 days previously.[13] Unsatisfactory assay subjects were about equally divided into 2 groups. One group of animals gave no pressor response or practically none (less than 10 mm of Hg) with the foregoing or larger doses of renin. The other was composed of dogs which gave a pressor response to the first injection and none to subsequent injections, frequently with a failure of the blood pressure to return to its original level.

Splanchnic stimulation was performed on the peripheral end of the nerve on one side for a total of 1 to 4 hours in a group of dogs by means of a shielded electrode and a Harvard inductorium set at 6 cm, with 2 dry cells and an interrupter which permitted alternate minutes of tetanization in the primary circuit. The non-stimulated, control kidney was removed prior to the period of stimulation in some of the dogs. A hypotension of 60-70 mm of Hg was produced and maintained for 2 to 4 hours by hemorrhage in another group of dogs following removal of one kidney as control. Both the splanchnic stimulated and the hypotensive dogs were anesthetized with sodium barbital.

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11 Grossman, E. B., PROC. SOC. EXP. BIOL. AND MED., 1938, **39**, 40.

12 Pickering, G. W., and Prinzmetal, M., *Clin. Sci.*, 1938, **3**, 211.

13 Merrill, A., Williams, J. R., Jr., and Harrison, T. R., *Am. J. Med. Sci.*, 1938, **196**, 18.

The renin content of one-half of a group of 24 normal dogs was such as to give an average pressor response for both kidneys of 21-30 mm of Hg in a dose of one-half g of kidney equivalent per kg of assay animal. The remaining dogs were about equally divided between dogs showing a renin content less than this median group and those with a renin content greater than the median. The maximum renin content observed (2 dogs) was about 3 times that of the median group, as judged by pressor effects of 61-70 mm of Hg. There was no correlation between these variations in the renin content and the blood pressure levels of the dogs. The renin contents of the 2 kidneys of the same dog were approximately equal in 19 of the animals (79%) but definite differences occurred in 5 of the dogs.

Unilateral stimulation of the splanchnic nerve (equally divided between right and left) in a group of 31 dogs produced no significant effect on the renin content of the stimulated as compared with the non-stimulated control kidney. Thus the renin contents of the 2 kidneys were approximately the same in 24 of the dogs (77%); in 4 instances the stimulated kidney showed a greater content than the non-stimulated control, and in 3 cases the reverse was true.

There was likewise no significant change in the renin content of the kidneys of the group of 6 dogs subjected to hypotension, when these kidneys were assayed against the opposite control kidneys. Thus, the renin contents of the 2 kidneys were approximately the same in all 6 dogs. Three of the hypotensive kidneys, however, showed an increased amount of depressor substances.

These results lend no support to the possibility that renin plays a rôle in the maintenance of normal blood pressure. Thus there was no correlation between the renin content of the kidneys of normal dogs and their blood pressure levels. The significance, if any, of the variations in the renin content of different dogs and, in some instances, of the differences between the 2 kidneys of the same dog, is not apparent at present. A decreased amount of renin in the kidneys of old rats has been reported,[14] but unfortunately the ages of our dogs were unknown. Prolonged stimulation of the splanchnic nerve did not alter the pressor activity of the corresponding kidney. Whatever the function of the nerve endings which penetrate the cells of the renal tubules may be, it is most likely not concerned with the formation or secretion of renin, if, indeed, the latter occurs. Lastly, the hypotension employed did not significantly alter the amount of renin. It must be emphasized, however, that these findings do not

[14] Grossman, E. B., and Williams, J. R., Jr., *Arch. Int. Med.*, 1938, **62**, 799.

exclude the possibility that renin plays a rôle in the maintenance of normal blood pressure.

Conclusions. 1. Bilateral nephrectomy under the above conditions increases the sensitivity of the dog to the pressor action of renin administered intravenously. 2. The renin content of the kidneys of dogs bears no relation to the blood pressure level of the animals. 3. Differences in the renin concentration of the kidneys of dogs and even between the 2 kidneys of the same dog, occur. 4. Stimulation of the splanchnic nerve produces no significant change in the renin content of the dog's kidney. 5. Hypotension as induced above does not alter significantly the renin concentration of the kidney of the dog. 6. There is no evidence at present for the possible rôle of renin in the maintenance of normal blood pressure.

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Effect of Protein Alimentation on the Secondary Sex Ratio of Offspring of Rats.

F. HOELZEL, ESTHER DA COSTA AND A. J. CARLSON.

From the Department of Physiology, University of Chicago.

The sex-determining theory which Geddes and Thompson[1] and others attribute to Girou, namely, that the better nourished parent tends to determine the same sex in the offspring, was tested by mating rats fed diets adequate or high in protein (containing 30% to 50% casein) with rats fed diets low in protein (containing 7.5% to 12% casein, but otherwise similar to the high protein diets). Albino, hooded and hybrid (hooded-albino) rats were used. When increases in weight suggested pregnancy, the females were isolated and placed on a stock diet. The sex of the offspring was determined within 24 hours after birth. A preliminary study which lasted 8 months during which 49 litters were obtained yielded some data supporting Girou's theory but needing further confirmation. Accordingly a further study was undertaken which thus far involved 15 months during which 652 litters were obtained.

In our main study, only one male was used for mating with the females in each of 7 groups including from 10 to 17 individuals. Thus we obtained from 52 to 126 litters from each male within a year. Genetic variables were also reduced to a minimum by using

[1] Geddes and Thompson, *The Evolution of Sex*, Revised Ed., London, 1904.