THE ACTION OF RENIN ON RABBITS WITH RENAL HYPERTENSION

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All evidence points to the production of hypertension from renal ischemia as being mediated by the liberation of a pressor substance into the blood stream by the kidney. In a recent paper Page (1) has summarized the experimental reasons for this belief. It is natural that renin, the pressor substance obtained from the kidney, should be suspected of being the actual chemical agent involved in the production of hypertension of renal origin. There is experimental evidence to support this view. Prinzmetal and Friedman (2) have reported a higher renin content in the kidneys of rabbits made hypertensive by renal ischemia. Harrison, Blalock and Mason (3) report similar results. There are some difficulties in the way of acceptance of this view. The action of renin is very brief, whereas the hypertension due to an ischemic kidney persists for many hours after the removal of the organ. Furthermore all animals quickly develop a tolerance to renin (4). This phenomenon has been given the name tachyphylaxis. It is difficult to understand how renin can cause hypertension which may last months, when the repeated injection of this substance results in a refractoriness to it of the animal in an hour or so. However, Page (1) and Hill and Pickering (5) have recently reported that the steady intravenous infusion of renin at a small dosage per minute results in a sustained elevation of blood pressure.

It appeared to us that observations of the action of renin on hypertensive animals would aid in clearing up this question. We planned to determine the degree of sustained hypertension that can be produced by renin, to contrast such a hypertension with renal hypertension, to compare the responses of the hypertensive and normal animals to renin, and to investigate tachyphylaxis in normal and hypertensive animals.

Methods and Materials

We used rabbits throughout. We produced hypertension in them by the method of Drury (6). Renins of different types were used in the experiments. The methods

used were those of Pickering and Prinzmetal (7) and of Helmer and Page (8). The type used in each experiment will be specified in the protocols. Blood pressures were recorded by means of a mercury manometer connected with a cannula in the carotid artery; the figures for blood pressure given in the paper are obtained from the kymograph records and represent mean arterial pressures.

Comparison of the Effects of Renin in Normal and Hypertensive Animals

We studied the action of renin in hypertensive rabbits and compared it with control findings in normal animals. The blood pressure response of the hypertensive animal is qualitatively similar to that of the normal. This is shown in Fig. 1 which illustrates the effect in the two types of animal. The same similarity in response obtains for larger doses. In Table I we have

TABLE I

Type of animal	Type and amount of renin		Initial pressure	Rise in pressure	Total area of blood pressure effect
		cc.	*mm. Hg*	*mm. Hg*	*sq. cm.*
Normal	P + P	0.5	84	20	6.0
Hypertensive	P + P	0.5	174	50	11.2
Normal	H + P	0.05	100	28	5.2
Hypertensive	H + P	0.05	158	24	5.7
Normal	H + P	0.05	94	28	6.6
Hypertensive	H + P	0.05	140	22	5.2

P + P = Pickering and Prinzmetal.
H + P = Helmer and Page.

attempted to give a quantitative comparison of the maximum pressure rises and of the areas between the tracings of the total blood pressure effects and the base line representing the pressure present before injection in hypertensive and normal rabbits given the same doses of renin. One can note that on the average the results show no essential difference in response between the two types of animal.

Degree of Sustained Hypertension Produced by Renin

Hill and Pickering (5) report that a sustained increase in blood pressure can be produced in rabbits by the continued infusion of renin at the rate of 0.2 units per 10 minutes. The definition of a unit is rather rough, but according to Pickering and Prinzmetal (7) a quarter of a unit produces a rise of 20 to 30 mm. Hg in the adult rabbit. With the renin preparation we used

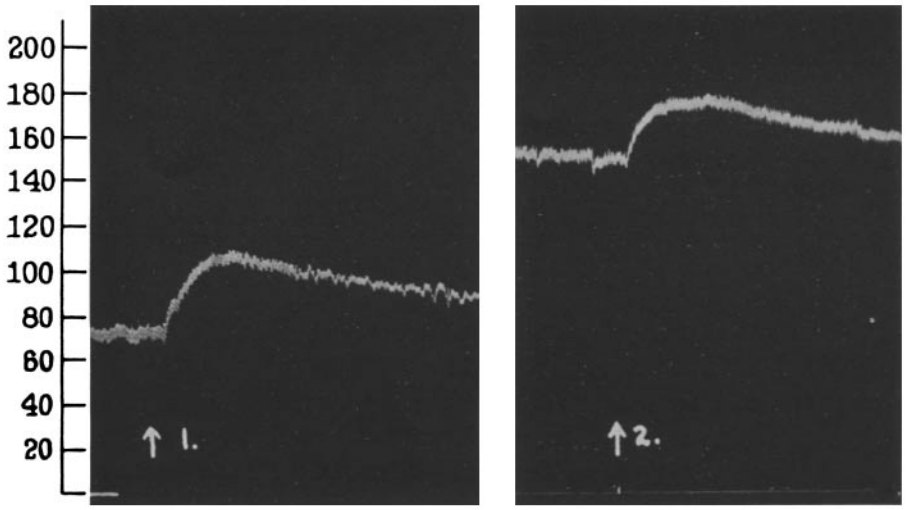

FIG. 1. Comparison of the effect of renin in normal and hypertensive rabbits. Arrow 1 marks the injection of 0.1 cc. of renin (Helmer and Page) into a normal rabbit. Arrow 2 indicates the same dose injected into a hypertensive animal.

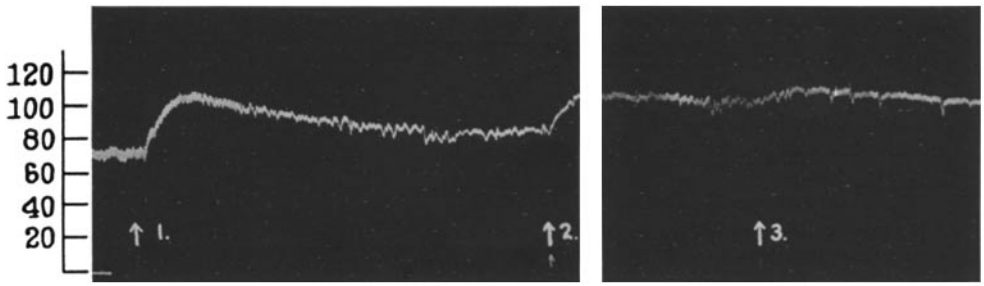

FIG. 2. Continuous infusion of renin into a normal rabbit and its effect on the response to subsequent injections. Arrow 1 indicates the preliminary injection of 0.1 cc. of renin. A continuous infusion of renin (0.1 cc. per 10 minutes) was begun at arrow 2. The break in the record represents a 15 minute interval. Arrow 3 indicates a superimposed quick injection of 0.1 cc. of renin.

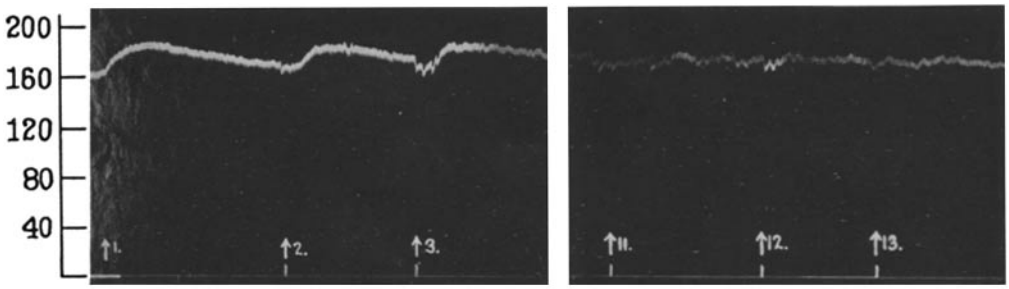

FIG. 3. Development of tachyphylaxis in a hypertensive rabbit. Arrows 1, 2 and 3 mark the injections of 0.1 cc. of renin. The break in the record represents a 30 minute interval during which 7 doses of renin totaling 1.0 cc. were given. Arrows 11, 12 and 13 mark the injections of 0.2 cc. of renin at 6 minute intervals.

(Page and Helmer) we produced an average rise of 25 mm. Hg with injection of 0.1 cc. When we injected such a solution into a rabbit at the rate of 0.1 cc. (diluted with 2 cc. of saline) per 10 minutes we obtained a sustained rise in blood pressure. In Table II we have assembled our results. It is apparent from these that the maximum sustained rise obtained was 28 mm. Hg. The injection of renin at rates which gave higher blood pressures resulted in tachyphylaxis which prevented the maintenance of the higher levels. Neither the levels that could be sustained nor even the higher ones which could not be maintained approached the degree of hypertension shown by many of our rabbits with renal ischemia. The measurements of these are given in Table IV under "Initial mean pressure." It can be seen that 4 of these animals had pressures of 160 mm. Hg or over,

TABLE II

Effect of Constant Infusion of Renin (Helmer and Page)

Rate of infusion	Initial pressure	Rise
	mm. Hg	*mm. Hg*
Given 0.2 cc. renin per 10 min.	101	19
Given 0.1 cc. renin per 10 min.	94	13
Given 0.1 cc. renin per 10 min.	87	25
Given 0.2 cc. renin per 10 min.	75	28
Given 0.2 cc. renin per 10 min.	81	20
Given 3.2 cc. renin per 10 min.	89	49*

* Rise in pressure not sustained.

whereas the highest level which we obtained with renin was 138 mm. Hg and this was not enduring, the highest sustained level being 120 mm. Hg.

Animals in which we were maintaining a raised blood pressure by constant injection of renin were given a superimposed quick injection of 0.1 cc. of our renin solution, the amount that is to say which would give a rise of 20 to 30 mm. Hg in the normal animal. The response of these animals differed quite markedly from that of a normal one. The superimposed rise is quite small and comes on more gradually than the normal response. This is illustrated in Fig. 2. A similar result was obtained on another animal that responded to an injection of 0.1 cc. renin with a rise in blood pressure from 87 mm. Hg to 113 mm. Hg. This animal was then given a constant infusion of renin at the rate of 0.1 cc. per 10 minutes which resulted in a sustained blood pressure level of 101 mm. Hg. Thereupon a superimposed injection of 0.1 cc. renin caused an additional rise of 6 mm. Hg. Such a response differs markedly from that of the rabbits hypertensive from renal ischemia in which the reaction to such an injection is similar to that obtained in a normal animal as previously illustrated in Fig. 1.

This decrease in response in animals with raised blood pressure levels caused by constant renin injection is undoubtedly related to a characteristic of renin already described by Pickering and Prinzmetal (7). These workers have shown that the ratio between size of dose of renin and size of response is not linear but decreases rapidly as the amount of the dose is made larger. They believe the relationship to be logarithmic. The fact that our renal hypertensive rabbits respond quantitatively like normal animals is therefore evidence against the theory that renin is the causative agent of their hypertension. If a large constant secretion of renin from the kidney were the cause of their hypertension, a superimposed dose of renin given by the experimenter would result in a reduced response, which is not the case.

TABLE III

Tachyphylaxis to Renin (Helmer and Page) in Normal and Hypertensive Rabbits

Animal	No. of doses of renin required for complete tolerance	Total quantity required for complete tolerance	Initial mean blood pressure	Final mean blood pressure	Change in mean blood pressure
		cc.	*mm. Hg*	*mm. Hg*	
Normal 1	11	2.0 (dialyzed)	100	102	2 mm. rise
Hypertensive 1	12	1.5 (dialyzed)	158	178	20 mm. rise
Normal 2	13	2.5 (undialyzed)	94	94	0 change
Hypertensive 2	14	4.1 (undialyzed)	140	142	2 mm. rise

Production of Tachyphylaxis in Hypertensive Rabbits

In 2 hypertensive and in 2 control normal rabbits we produced tachyphylaxis by repeated injections of renin. The animals were done in pairs; for each hypertensive rabbit we carried out a control animal of similar weight and gave the same renin and in similar doses. Comparisons of the two were made with regard to number of doses and total renin necessary to produce absolute tachyphylaxis (that is complete lack of response). We also determined the blood pressure after complete tolerance had set in and compared that with the level before any administration of renin.

These results are given in Table III. The similarity in response of hypertensive rabbits to normal ones is evident. The most significant point is the fact that the level of blood pressure of the hypertensive animals after tachyplaxis has been produced, has not been decreased from that

which the animals had before any injection of renin. The blood pressure level of the normal rabbits was unaffected by the procedure. Similar results were obtained in an additional group of 3 normal and 4 hypertensive animals, which are recorded in Table IV. It is apparent that as the animals become tolerant or refractory to renin the basic blood pressure does not decrease. We illustrate this point in Fig. 3 taken from the results of one of the hypertensive animals.

An explanation for tachyphylaxis given by those believing that renin is the renal hypertensive agent, is that all preparations of this substance must contain a depressor material. The preparations of Tigerstedt and of

TABLE IV

Tachyphylaxis to Renin (Helmer and Page) in Normal and Hypertensive Rabbits

Animal	Initial mean blood pressure	Final mean blood pressure after tachyphylaxis	Change in mean blood pressure
	mm. Hg	*mm. Hg*	
Normal 3	104	112	8 mm. rise
Normal 4	120	100	20 mm. fall
Normal 5	90	90	0 change
Hypertensive 3	188	178	10 mm. fall
Hypertensive 4	174	178	4 mm. rise
Hypertensive 5	160	160	0 change
Hypertensive 6	178	174	4 mm. fall

Average change of blood pressure for 5 normal and 6 hypertensive rabbits 0.2 mm. rise.

certain others actually produce a drop in blood pressure before the rise due to the renin. Other preparations such as those of Landis, Montgomery and Sparkman (9), and of Helmer and Page (8) do not exhibit this. Renin prepared by the method of these last investigators is highly refined chemically and probably contains very little impurities. However it produced tachyphylaxis like any other preparations. Another point against the depressor-contaminant theory for tachyphylaxis, is that renins prepared by a great variety of procedures all produce the effect. If there were a depressor-contaminant it would have to have chemical properties practically identical to those of renin. The possibility still exists however, that all preparations of renin as prepared from kidneys contain a slowly acting depressor substance or one antagonistic to renin. In order for such a substance to be responsible for the production of tolerance to renin it would

have to last a comparatively long time in the body (an hour or so). We could explain the production of tolerance then by supposing that each successive dose of renin administered carried with it a certain amount of this depressant, or antagonist, which, because of its persistence in the body, gradually builds up and eventually has sufficient effect to counteract entirely any of the pressor portion of the injected renin. If such be the case, the hypertension of renal ischemia cannot be caused by renin, since if it were so the blood pressure of our hypertensive rabbits would have steadily declined with the production of tachyphylaxis; this would be occasioned by the accumulated antagonist acting on the renin constantly being secreted by the kidney which is supposedly causing the original hypertension.

DISCUSSION

Hill and Pickering (5) in their recent work which supports the concept that renin is the mediator of the hypertension of renal ischemia report that they have produced the same degree of hypertension with infusion of renin as they caused by renal artery constriction. They measured blood pressure in the ear artery by means of Grant's capsule (10). This gives the systolic value in this vessel; we measured the mean arterial pressure in the carotid. The amount of rise in blood pressure caused by the infusion of renin which they report (20 to 30 mm. Hg) agrees with that which we obtained. However the increase in blood pressure which they produced by renal ischemia (30 mm. Hg in systolic pressure of ear artery) is much less than the increase of mean carotid pressure of our hypertensive rabbits over normal (80 mm. Hg). The discrepancy in these results may be due to the difference in the methods used for measuring blood pressure or in the difference in the procedures used for production of hypertension in the rabbit. Whatever may be the explanation, our contention still stands. We have been able to increase the sustained mean pressure of the carotid artery by not more than 30 mm. Hg with renin, whereas with renal ischemia we have produced increases in mean pressure of the carotid of 80 mm. Hg above normal.

One could hardly deal with the subject of renal hypertension without referring to the recent interesting discoveries of Page and his coworkers (1). One would want more complete knowledge in this field before correlating our findings with theirs. However, they have shown that pure (dialyzed) renin has no constrictor effect on peripheral blood vessels such as those of the dog's tail or rabbit's ear and that in order to act on these it is necessary for it to have the cooperation of a substance present in blood which they call renin activator. They show that if these tissues be perfused with

blood the addition of renin will cause constriction at first but additional doses of renin have less and less action. If then renin activator is added with a dose of renin the constrictor action is restored. When a similar experiment is carried out with the entire animal, that is if renin plus renin activator be injected into an animal that has been made tachyphylactic, there is no rise in blood pressure. Their results would seem to give an explanation of "tolerance" in isolated peripheral blood vessels but not for the entire animal. There is today no evidence for the conclusion that renin hypertension is produced only by an increased resistance of peripheral vessels. The findings of Page and his associates are of great interest to anyone engaged in hypertension research and are of definite importance in the field of blood vessel physiology. However at the present time we do not believe that their results can change the validity of our conclusions that renin in any of the forms which we used is not by itself the cause of the hypertension in rabbits produced by renal ischemia.

SUMMARY

Our results lead us to believe that renin in the form in which it is extracted from the kidney cannot be the agent causing chronic renal hypertension.

The reasons against accepting renin as the pressor substance responsible for the hypertension of renal ischemia may be summed up as follows:—

1. The high blood pressure levels of renal ischemia cannot be approximated by any constant injection of renin that will maintain a sustained increase in normal animals.

2. The ratio of size of response to size of dose becomes progressively less as the amount of the dose is increased. If the hypertension of renal ischemia were due to a large elaboration of renin in the body, a small dose injected would be expected to have much less effect than in a normal individual. This is not the case; the response of the hypertensive animal to a given dose of renin is the same. Also animals with increased blood pressure due to a constant infusion of renin respond differently qualitatively and quantitatively to renin than do animals hypertensive from renal ischemia.

3. Since renin exhibits the phenomenon of tachyphylaxis one cannot explain the sustained hypertension of renal ischemia as due to a substance toward which the body becomes refractory as more and more of it is given. If tolerance results from the presence in the renin preparation of an antagonistic contaminant which persists longer in the body than the pressor agent, renal hypertension is definitely not caused by renin. This follows from our observations that rabbits hypertensive from renal ischemia, and in which

tolerance is produced, maintain the blood pressure they had before injection of any renin.

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